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A Systematic Review of Associations between Environmental Exposures and Asthma Causation in Children Aged up to Nine Years

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ABSTRACT

Objectives. Childhood asthma is a complex condition where many environmental factors are implicated in causation. The aim of this study was to complete a systematic review of the literature describing associations between all environmental exposures and asthma causation in young children.

Setting. A systematic review of the literature up to November 2013 was conducted using key words agreed by the research team. Abstracts were screened and potentially eligible papers reviewed. Papers describing associations between exposures and exacerbation of pre-existing asthma were not included. Papers were placed into the following predefined categories: second hand smoke(SHS), inhaled chemicals, damp housing/mould, inhaled allergens, air pollution, domestic combustion, dietary exposures, respiratory virus infection and medications.

Participants. Children aged up to nine years.

Primary outcomes. Diagnosed asthma and wheeze.

Results. 14,691 abstracts were identified, 207 papers reviewed and 135 included in the present review of which 15 were systematic reviews, 6 meta analyses and 14 were intervention studies. There was consistent evidence linking exposures to SHS, inhaled chemicals, mould, ambient air pollutants, some deficiencies in maternal diet and respiratory viruses to an increased risk for asthma (odds ratio typically increased by 1.5-2.0). There was less consistent evidence linking exposures to pets, breast feeding and infant dietary exposures to asthma risk. There was good evidence that exposures to house dust mite (in isolation), postnatal antibiotics and paracetamol were not associated with asthma risk. Evidence from observational and intervention studies suggest that interactions between exposures were important to asthma causation, where the effect size was typically 1.5-3.0.

Conclusions. There are many publications reporting associations between environmental exposures and modest changes in risk for asthma in young children and this review highlights the complex interactions between exposures which further increases risk.

Strengths and limitations of this study

- This is the first systematic review of the whole literature relating early life environmental exposures to childhood asthma causation
- A high level of evidence was available (i.e. systematic reviews, meta analyses and/or intervention studies) for many exposures classes
- More than 70% of papers identified described associations observed within single populations
- The observational literature is likely to be affected by publication bias, reverse causation and confounders.
- Studies describing outcomes in children where the mean age was >9 years were not included

INTRODUCTION

Asthma is a common chronic condition in children where environmental and genetic factors are implicated in causation. The rapid rise in asthma during the 1980s and 1990s [1] was too abrupt to be explained solely by change in prevalence of genetic variations. Changing environmental exposures appear to be relevant to the high prevalence of asthma in the Western world [2], although some exposures are likely to be effective via epigenetic mechanisms [3]

Many environmental exposures have been linked to asthma causation, including allergens [4], smoking [5], dietary factors [6] and respiratory infections [7]. More recently, evidence has emerged to suggest that asthma causation may involve interactions between different environmental exposures [8,9] and/or environmental exposures and atopy [10]. Due to the many challenges of relating even a single exposure to asthma causation, there is very little synthesis in the literature of multiple environmental exposures and asthma causation.

The Environmental Determinants of Public Health in Scotland (EDPHiS) was commissioned in 2009 to quantify the evidence on the connections between the environment and key aspects of health of children in order to inform the development of public policy. Asthma was identified as a priority along with obesity, unintentional injury and mental health. The overall aim of this systematic review was to capture all of the literature associating early environmental exposures and asthma development in children up to nine years of age; this cut off was chosen to avoid the effects of puberty and active smoking on asthma causation. A recent paper describes associations between environmental exposures and asthma control and exacerbation[11]. Our specific aims were (i) to describe the magnitude of association between asthma causation and environmental exposures (ii) to explore evidence of interactions between environmental exposures.

METHODS

Study design

A workshop attended by senior researchers from government and academia, health practitioners and policy professionals identified environmental influences considered important to on causation and exacerbation of asthma (previously described[11], Table I). By extrapolation from approaches to assessment of causation in workplace exposures for compensation purposes (http://iiac.independent.gov.uk/about/index.shtm), we considered an exposure which increased the risk for asthma by at least two-fold as having at least a modest effect size.

Search strategy and data sources

The search strategy for Medline is provided in the supplement and has also been described previously[11]. Two reviewers (SD and ED) searched the electronic databases (including Medline, Embase, Cochrane controlled trials register (CCTR) and CINHAL) and reference lists of other studies and reviews between January 2010 and April 2010. Updated searches were carried out in July 2011 and November 2013. No date limits were applied to the search strategy. Studies identified from searching electronic databases were combined, duplicates removed and papers were screened for relevance to the review based on the information contained in the title and abstract. Abstracts were screened by a second reviewer (ST) and potentially eligible papers were identified.

Inclusion/ exclusion criteria

Studies were included if a) they captured exposure to an environmental factor identified as potentially relevant to asthma causation b) the mean age of asthma outcome was <9 years, outcomes include diagnosis of asthma or data related to health care utilization (hospital admissions, drug use) and morbidity and functional status, lung function tests, measures of self-perception of health status (symptom free days) and wellbeing and quality of life; c) the study design was either a meta analysis, systematic review, randomized control trials, non randomized control trials and

cohort studies. If no evidence was apparent for an exposure, then studies meeting the lower Scottish Intercollegiate Guidelines Network criteria were considered, i.e. case control and case report studies (http://www.sign.ac.uk/guidelines/fulltext/50/annexb.html 21st June 2014). Clinical trials were excluded.

Study selection and data extraction

The full text of references identified as potentially relevant were obtained and papers included by applying the inclusion criteria, sometimes after discussion between reviewers (SD and ST). Papers which were included in a systematic review were not included. For cohort studies where outcomes were reported at increasing ages after one exposure, only the most recent paper was included. A summary table included the following details from studies: study design, characteristics of the study population, the study objectives, the key outcome(s) reported including what the primary asthma outcome, eg wheeze, physician diagnosed asthma.

Quality assessment

Quality assessment of included papers was carried out using "Effective public health practice project quality assessment tool for quantitative studies" (http://www.ephpp.ca/PDF/Quality%20Assessment%20Tool_2010_2.pdf Accessed June 2014**).** Results are presented in the supplement, due to the relatively large number of studies identified a random 10% were chosen for quality assessment.

RESULTS

Literature search

There were 14691 references identified from electronic databases and other studies. There were 207 full papers reviewed and 135 studies met the inclusion criteria (Figure 1). There were 15 systematic reviews, 6 meta analyses, 91 cohort studies, 14 intervention studies included, 5 case-

control studies and 3 cross sectional studies. There no case series was included. There were 61 studies from Europe (including 3 meta analyses), 32 from North America, 13 studies from Australia or New Zealand, 3 from Japan and single remaining papers from UAE, India, Qatar, South Korea, Mexico, Taiwan and Brazil. There were 84 (63%) studies published in the last five years, i.e. from 2009. Table 1 in the supplementary file presents details of the included studies, including number and mean age of children included, the respiratory outcome reported and the effect size. No studies were identified for industrial combustion, fireworks, bonfires, vacuuming, air conditioning or air humidifiers. Table 2 presents the effect size of the exposures on asthma risk from the studies identified. Table 3 presents results from studies where interactions between exposures were associated with altered asthma risk

Second Hand Smoke

Antenatal exposure

One meta analysis and five cohort studies were identified and most found exposure was associated with increased risk for asthma. The meta analysis[12] identified 735 exposed children and concluded that exposure was associated with an increased risk for asthma at six years (OR 1.7). The cohort studies found risk was increased by 1.13[13] and 2.1[14] at 2 years and 1.4 at seven years[15]. One study of infants born 3-4 weeks prematurely found increased risk for wheeze at three years only among those exposed to SHS (odds ratio 4.0, table 3) [16]. One study found no association between antenatal exposure and risk for symptoms[17].

Post natal exposure

One systematic review and six cohort studies were identified and all reported that exposure was associated with increased asthma risk. The systematic review concluded that exposure to tobacco smoke was associated with an increased risk of 1.3 among children aged 6-18 years[5]. Postnatal exposure was associated with increased risk for wheeze between 1.2 [18] and 2.9 [17] and asthma at five

years 1.7 (table 3)[19]. The study from Japan[17] found a link between postnatal but not antenatal maternal smoking and wheeze at 16-24 months. One study [18] found that postnatal paternal smoking was a risk factor for wheeze (RR 1.14 [1.04-1.24]) independent of maternal smoking. Another study reported an interaction between short duration of maternal education and SHS exposure[19]. A final study found that increasing exposure to fine particulates ($PM_{2.5}$) and urinary cotinine, products of tobacco combustion, were positively linked to risk for infant wheeze[20].

Domestic combustion

Two cohort, one cross sectional and two case-control studies were identified and there was inconsistent evidence between exposure and asthma risk. One cohort study retrospectively modelled exposure to gas cooking at five years to asthma in four year olds and found no association[21]. In a second cohort study, increasing exposure to domestic $PM_{2.5}$ was associated with increased risk for new onset wheeze over the next three years (OR 1.5 per quartile increase in exposure), adjusting for SHS exposure[22]. A cross sectional study found an association between detectable indoor air sulphur dioxide (SO_2) and risk for wheeze (OR 1.8) at age six-ten years[23]. This study found no link between burning incense and asthma symptoms[23] and this was consistent with a case-control study which found no evidence for exposure to Bakhour incense and risk for asthma [24]. A case-control study from India[25] found evidence for increased asthma among children (OR 4.3) living in homes where biomass was used for cooking compared to other homes.

Inhaled Chemicals

One meta analysis, one cohort study, one cross sectional study and two reports from one case-control study were identified and all found evidence of exposure being associated with increased asthma risk. The meta analysis of data from seven studies concluded that increasing formaldehyde exposure was associated with increased asthma risk (OR 1.2 per 10µg/m^3 increase)[26]. A cohort study[27] used redecoration of the apartment as a proxy for exposure to volatile organic compounds

(VOCs) and found an increase in risk for obstructive bronchitis (OR 4.2). Simultaneous exposure to ETS and cats added to the risk (OR 9.1, table 3)[27]. One cross sectional study [28] found an association between indoor exposure VOC of microbial origin (MVOC's) and plasticizers and risk of asthma (mean increased risk for asthma 2.1 per microg/m^3 of total MVOC). Two scientific papers on the same study[29,30] found domestic exposure to formaldehyde, benzene and its compounds and toluene was positively associated with asthma risk (3% increase per 10 microg/m^3 increase in formaldehyde exposure).

Chlorinated swimming pools

Three cohort studies were identified and results were apparently conflicting. Exposure to chlorinated swimming pools in infancy and childhood was associated with reduced risk for current asthma at seven years (OR 0.5)[31]. A second study found no link between exposure to chlorine through swimming and asthma at six years of age[32]; those who did not attend swimming during the first year of life were more likely to have asthma.

Other chemicals

In this broad category there was one systematic review, two cohort studies, two cross sectional studies and a case-control study; all found evidence of exposures being linked to increased asthma symptoms. A systematic review of seven studies of children aged up to 12 years found a positive association between polyvinyl chloride exposure in dust samples and asthma (OR 1.6) [33]. One study (using the same cohort mentioned above[31]) created a composite household chemicals exposure score (including chlorine/chloride exposure), and found a positive association between exposure and risk of incident wheeze after 2.5 years of age (OR 1.7)[34]. Two cohort studies related antenatal and current exposures to asthma risk: high exposure to pyrene was associated with increased asthma risk in 5-6 year olds (OR 1.9)[35], and this association was only apparent in non-atopic children and maternal exposure during pregnancy was not related to asthma (table 3); maternal Bisphenol A exposure during pregnancy was inversely associated with wheeze at five years (OR 0.7) but not at seven years, however the child's current exposure was positively association with this outcome (OR

1.4)[36]. Living close to a petrochemical plant was associated with an increased risk for asthma (OR 2.8) [37]. A case-control study found increased wheeze in 6-14 year olds living close to an oil refinery compared to controls (OR 1.7)[38].

Damp housing/mould

One systematic review, one meta analysis plus four cohort studies were identified and early exposure was consistently associated with increased risk for later asthma symptoms. The systematic review included data from 16 studies and concluded that exposure to visible mould was associated with increased risk for asthma (OR 1.5) [39]. The meta analysis of 8 European birth cohorts found an association between exposure to visible mould or dampness and increased wheeze at two years (OR 1.4) but not significantly at 6-8 years (OR 1.1)[40]. The cohort studies found mould exposure in early life to be associated with increased risk for asthma at three years (OR 7.1) [41] and seven years (RR 2.4 for presence of any mould[42] and OR of 2.6[43] and 1.8 [44] per unit increase in mouldiness index).

Inhaled allergens

Indoor exposures

Multiple exposures

There were five intervention studies and eight additional cohort studies identified. One intervention randomised newborns to house dust mite (HDM) reduction measures, avoidance of cows milk or both or neither and found no difference in asthma incidence at age five years across the four groups[45]. A second study also modified post natal exposure to cows milk protein (and other dietary allergens) and HDM and the intervention group had trends for reduced wheeze (OR 0.4 [0.2, 1.08]) at eight years[46]. A third intervention study reduced exposures to SHS, inhaled and ingested allergens and promoted breastfeeding but found no difference in asthma outcome age six years[47]. The fourth intervention modified exposures to antenatal and postnatal oily fish, SHS and dampness and observed reduced asthma risk at two years for the intervention group (OR 0.7)[48]. The fifth study

modified antenatal and postnatal exposures to HDM, pets, SHS, promoted breast feeding and delayed weaning and asthma risk at seven years was reduced in the intervention group (OR 0.4)[49]. Five observational studies related early life HDM exposure plus other "dust" exposures to asthma: increased HDM and LPS exposures were independently associated with increased symptoms by seven years; HDM ≥10 microg/g associated with increased risk for asthma (OR 3.0) and each quartile increase in LPS associated with increased risk for lifetime wheeze(OR 1.2) [50] and exposure to higher concentrations of cat allergen (but not to HDM) and asthma by six years of age OR for third versus lowest exposure quartile 2.6 [1.3, 5.4] [51]; other studies found no association between (i) infantile exposure to HDM and cat and cockroach allergen and wheeze at two years[52] (ii) HDM, cat and dog allergen exposure and wheeze at four years[53] and (iii) HDM and cat exposure and asthma at seven years [54]. One study reported increasing cockroach allergen exposure in infancy was positively associated with wheeze by age five years (OR 1.8) and, independently, the presence of a dog and higher concentrations of cat allergen exposure were associated with reduced wheeze risk (OR 0.3 and 0.6)[55]. Dog allergen exposure in infancy was not associated with asthma at seven years *per se* but was associated with asthma in combination with exposure to SHS (OR 2.7) or elevated NO_2 (OR 4.8) [56]. A final study observed interactions between exposures to SHS, breast feeding and recurrent respiratory infections and asthma[57].

Pet exposure

There were two systematic reviews, one meta analysis and six cohort studies identified and the results were highly inconsistent. One systematic review of nine studies concluded that exposure to pets around the time of birth may reduce risk for allergic disease (including asthma) where there is no family history of asthma, but no effect size was given[58]. The second systematic review concluded that exposure to cats reduced the risk for asthma (OR 0.7) and to dogs increased asthma risk (OR 1.1)[59]. The meta analysis found no evidence for cat exposure in early life being linked to asthma risk at age 6-10 years, there was a non-significant trend for dog ownership to be associate with reduced asthma risk (OR 0.8 [0.6, 1.0]) [60]. The cohort studies found early cat exposure to be associated with

increased severe asthma at four year (OR 4.7)[61], and reduced wheeze by age five years (OR 0.6[62] and 0.3[63]), increased wheeze at seven years (OR 1.2) [64] and not association with asthma risk at four[65] or eight years[66] ; in a post hoc analysis early exposure to dog was linked to reduced late onset wheeze at 4 (OR 0.4 [0.2, 1.0])[65]. There was apparent synergy between exposure to both high concentrations of cat allergen and increased risk for severe asthma at 4 years (OR 10.8 [2.0, 59.6]) [61].

Other exposures

There was one systematic review relating exposure to living on a farm to asthma risk, data from 39 studies were identified and despite differences in definitions for asthma and associations with exposure to living on a farm, there was a 25% reduction in risk for asthma for children living on a farm compared to controls (no confidence intervals presented)[67]. A cohort study found an association between lipopolysaccharide (LPS) concentration in mother's mattress when the infant was three months old was associated with repeated wheeze by two years of age (OR 1.5 comparing highest with lowest quartile for exposure)[68]. A second cohort study reported an association between increased current exposure to mouse allergen and wheeze at seven years of age (OR 1.4)[69] ; there was no association between mouse allergen exposure in infancy and later wheeze. A third small cohort reported no association between exposure to cockroach allergen in infancy and wheeze in the first two years of life [52]. Observational studies report associations between exposure to feather quilt in infancy and reduced asthma at four years compared to non-feather quilt (OR 0.4)[70] and that a greater number of synthetic items of bedding (known to be HDM rich) during infancy was associated with increased risk for a history of asthma by 7 years (OR 1.8)[71].

House dust mite exposure

There were two intervention studies[72,73] and one observational study[74] and none found an association between exposure in infancy[72,73] or by two years of age[74] and asthma at 3[73], 6-7[74] or eight years of age[72].

Outdoor allergens

Three cohort studies were identified and all found exposure was related to increased asthma risk. One study related fungal spores and pollen concentrations at the time of birth to wheeze at age two years over 12 months in certain months of the year and those born in autumn to winter (the fungal spore season) were at increased risk for wheezing (OR 3.1)[75]. A second study reported an association between increased grass pollen exposure between 4 and 6 months of age and increased asthma at seven years of age (OR 1.4)[76]. The third study related tree canopy cover (a source of tree pollen and also of altered airflow and air quality) in infancy to asthma at seven years and found a positive association (RR 1.2)[77].

Air pollution

There was one meta analysis and eight additional cohort studies and whilst pollutants associated with combustion were associated with increased asthma risk, no single pollutant was consistently identified. The meta analysis found that exposure to Nitrogen dioxide (NO_2, OR 1.05), Nitric Oxide (OR 1.02), and Carbon Monoxide (CO, OR 1.06) were associated with higher prevalence of diagnosis of childhood asthma. Exposures to SO_2 (OR 1.04) and particulates (OR 1.05) were associated with a higher prevalence of wheeze in children[78]. Ambient lifetime CO exposure, but not NO_2, ozone or particulates with mass less than 2.5 microns ($PM_{2.5}$), was associated with increased risk for wheeze at five years (OR 1.04 per ppm increased CO)[79]. A second cohort study found that ambient exposure to NO_2, but not ozone, SO_2, $PM_{2.5}$ and PM_{10}, was associated with increased asthma risk at three years (OR 1.2 per 5ppb increase) [80]. A third study related averaged life time exposure to ozone, CO, NO_2, SO_2 and PM_{10}) and found no association with asthma in seven year olds for the whole population but among the 10% with previous bronchiolitis asthma risk was increased (OR approximately 7) in association with higher exposures to ozone, CO and NO_2[81], table 3. Exposure to traffic related particles (elemental carbon attributable to traffic) during infancy was associated with increased risk for asthma in three-year-olds (OR 2.0) and co- exposure to high concentrations of

domestic endotoxin increased the risk (OR 3.4) [82]. One study one found increased wheeze prevalence in four year olds among those exposed to stop/go traffic compared to unexposed children (23% versus 11%)[83] and the second found that children with a life time exposure to higher traffic density were more likely to be diagnosed with asthma (OR 1.3)[84]. Exposure to high (> 4.1μg/m^3) levels of $PM_{2.5}$ during infancy were associated with increased risk for asthma in a small cohort (OR 3.1)[85].

Dietary exposures

Maternal diet – food items

There was one systematic review, one intervention study and five cohort studies identified and some food items were linked to childhood asthma risk. The systematic review of 62 studies concluded that there was more convincing evidence for maternal fruit (compared with vegetable) intake during pregnancy to be associated with reduced risk for childhood asthma[86], there was only one study identified relating maternal Mediterranean diet to outcome (persistent wheeze (OR 0.2) at age 6.5 years) and maternal exposure to fish was not included. A small intervention study where pregnant mothers took placebo or fish oil supplement found no difference in respiratory symptoms between treatment groups at one year[87]. A study from Japan found reduced risk for wheeze at 16-24 months for children whose mother's diet had been least "Westernised" (OR 0.6 for comparison with most Westernised)[88]. A Mexican study found a protective effect of fish consumption during pregnancy on atopic wheeze (OR 0.6)[89]. In Denmark, maternal intake of peanuts (OR 0.8) and tree nuts (OR 0.8) was inversely associated with asthma in children at 18 months of age[90]. In Finland, low maternal consumption of leafy vegetables (OR 1.6), malaceous fruits (eg apple, pear, OR 1.5), and chocolate (OR 1.4) were positively associated with the risk of wheeze in five-year-old children[91]. A final study found no association between maternal butter and margarine intake and asthma outcomes at five years[92].

Maternal diet- specific nutrients

There was one systematic review and 8 cohort studies identified and reduced exposure to some nutrients was associated with increased asthma risk. Meta analysis within the systematic review found that (i) increasing maternal vitamin D intake was associated with reduced risk for wheeze in the last year (OR 0.6, 4 studies) but not asthma at five years (ii) increasing maternal vitamin E intake was associated with reduced wheeze at 2 years (OR 0.7, 3 studies) (iii) increased maternal plasma vitamin A was associated with reduced asthma risk (OR 0.3, 2 studies) and (iv) no evidence for associations between maternal plasma zinc or selenium and asthma outcomes[86]. Of five cohort studies published after the systematic review, four found no evidence linking maternal plasma vitamin D[93-95] or vitamin D intake[96] and asthma; one study found an inverse association between cord plasma vitamin D and risk for wheeze, but not asthma, by age five year (OR 0.95 per 10 nmol/L increase)[97]. One study found maternal fatty acid intake during the third trimester was associated with asthma out come at five years (e.g. higher alpha-linoleic acid and palmitic acid intake associated with ~40% reduced risk) [98]. Other studies found no association between maternal dietary antioxidants[99] or folate[100] and vitamin A[101] supplementation and childhood asthma outcomes.

Exposure to milk during infancy

In addition to the previously described complex interventions where milk exposure was modified, a number of studies were identified where only milk was the exposure of interest and there was evidence that early milk exposure was related to altered asthma risk.

Breast milk. There was one systematic review with meta analysis, two cohort studies and one intervention study identified. Meta analysis of 31 studies found any breast feeding reduced risk for wheeze (OR 0.92) but increased risk for asthma (OR 1.10) [102]. Never breast feeding was associated with increased wheeze by four years (OR 1.4)[103] and exclusive breast feeding was associated with reduced in asthma risk at five (OR 0.9) [104] but not at six years of age. The intervention study found that prolonged breast feeding (up to the age of 12 months) was associated with reduced asthma at

four but not at six years of age[105]. Maternal margarine intake (but not fatty acid or fish intake) whilst breastfeeding was associated with increased risk for asthma at five years (HR 2.0)[98].

Cow's milk formula. There were one systematic review, two intervention studies and one observational study identified. A systematic review of 10 trials concluded that hydrolysed cow's milk formula, but not soya-based milk, reduced risk of wheezing in infancy (RR 0.4]) compared to standard cow's milk formula [106]. Modification of cow's milk formula either by a non-hydrolysing fermentation process or supplementation with fatty acids (arachadonic acid or Docosahexanoic acid) was associated with reduced risk for wheeze by two (13 vs 35%)[107] and three years of age (OR 0.3)[108] compared to standard cow's milk formula. An observational study found no evidence for hydrolysed feed for the first six months reducing asthma risk at three years[109].

Dietary exposures during infancy

There were two systematic reviews, two clinical trials and five observational studies, there were some associations between exposure to some dietary components and altered risk reported. Four observational studies related first dietary exposures to asthma outcomes and one found evidence for early introduction of cereals by 6 months and egg by 11 months was associated with 30-40% risk for asthma at five years[110] and a second study found a direct relationship between age at introduction of oats and risk for asthma at five years (OR 0.4 for earliest versus latest age at introduction)[111]. Two other studies found no association between early or delayed introduction of any solids and asthma risk at 5[112] and 6 years[113]. A systematic review of 14 studies relating fish oil exposure during infancy and asthma (and other allergic outcomes) concluded that exposure was linked to a reduced risk of between 5 and 75%[114]. One cohort study found an association between the introduction of fish between 6 and 12 months and decreased risk for wheezing at 48 months (OR 0.6)[115] however the two previously discussed studies found no association between fish exposure and asthma[112,113] and an intervention study of fish oil supplements in the first six months of life did not change risk for asthma symptoms at 12 months [116]. A systematic review of two trials found no link between infant diet supplementation prebiotics and asthma risk[117], and a trial where infants

were randomised to supplement with probiotic (+/-prebiotic) or placebo also found no difference in asthma risk[118]. One cohort study found no evidence for association between infant vitamin supplements and asthma risk although among African-Americans, supplementation was associated with increased risk (OR 1.3) [119].

Dietary exposure in childhood

There were one RCT and six cohort studies identified and there was limited evidence linking early exposure to later increased asthma risk. Supplementation of milk with fermented milk containing lactobacillus during the first two years did not alter risk for asthma compared to placebo[120]. One observational study found daily exposure to full cream milk at two years reduced risk for asthma one year later (OR 0.6 [0.4, 0.9])[121]. Exposure to organic food during the first two years[122] and dietary oxidant at five[123] and were not associated with altered risk for wheeze at two years or asthma at eight years respectively. Studies from Netherlands found exposure to a "western" diet at 14 months was associated with a increased risk for frequent wheeze at three years (RR 1.5)[124], exposure to fruit in early childhood reduced risk for asthma at eight years (OR 0.93 per item consumed day per week) [125] and that increased plasma vitamin D at four years was associated with reduced asthma risk at eight years (OR for highest vs lowest tertile 3 0.5]) [126] but serum vitamin D levels at eight years were not associated with current asthma risk[126].

Respiratory virus infection

There were six cohort studies identified and there was consistent evidence for infection associated with wheeze or hospitalisation increased asthma risk. Parent reported lower respiratory tract infections during infancy were negatively associated with the risk of asthma at seven years of age in one cohort (OR 0.5) [127]. A cohort study demonstrated that wheeze before four years of age was associated with increased risk for asthma at six years if rhinovirus (OR 9.8) was present[128]; there was a borderline increase in risk if respiratory syncitial virus (RSV) was present (OR 2.6). A second cohort

selected for familial risk for atopy also found rhinovirus positive (but not RSV positive) wheezing lower respiratory tract infection during infancy was associated with increased risk for asthma at age five year (OR 2.9) [129]. A third study observed an increased risk of asthma following infection with RSV, and this risk was higher in the months following the hospitalization and lower with longer duration since hospitalization (e.g. RR 6.2 within two months of hospitalization and 2.2 6-11 months after hospitalization) [130]. Early day care, a proxy for respiratory infections, was not associated with altered risk for asthma at age eight years[131] in one cohort but was associated with reduced asthma risk at four years in a second study (HR 0.9)[132].

Other infections

One small cohort study observed reduced risk for wheeze at 18 months for children whose parents cleaned their dummy/pacifier by sucking it (OR 0.1 [0.01, 1.0]) compared to other cleaning practices [133]. A second cohort study found no evidence for infection in preschool children (either serologically proven or isolated from stool samples) and wheeze by 11 years [134].

Medications

Antibiotics

Three systematic reviews were identified which related antenatal [135] and postnatal [135-137] exposure to antibiotics and asthma outcomes. There was evidence that antenatal and postnatal exposure were associated with increased risk for early asthma symptoms (e.g. OR 1.2 for antenatal exposure and 1.5 for postnatal exposure)[135] but all three SRs concluded that this association was explained by reverse causation. One SR demonstrated that the OR fell from 1.3 to 1.1 when reverse causation was considered[136].

Paracetamol

Four SRs were identified and these linked antenatal [135,138] and postnatal [135-137] exposure to paracetamol to the risk of asthma symptoms. There were associations between paracetamol exposure and the development of asthma OR 1.3[139] and wheeze OR 1.2[138]. The third SR did not present an effect size and suggested that any association was by reverse causation[137].

Other maternal exposures during pregnancy

A whole-population study found treatment during the second and third trimester with the following were associated with increased risk for asthma ; antibiotics (OR 1.1) ; drugs for gastroesophageal reflux (OR 1.3); opiates (OR 1.6); thyroid drugs (OR 1.3); there was no association with paracetamol prescribing[140]. Five cohort studies related various maternal exposures during pregnancy to early childhood wheeze and reported the following associations: exposure to dietary dioxins and polychlorinated biphenyls was associated with increased wheeze by three years (OR 2.7) [141]; exposure to bisphenol A (BPA) was positively associated with a transient increase in wheeze in one study (OR for wheeze at six months 2.3, higher vs lowest exposure) [142] and inversely associate with transient wheeze in a second study (OR for wheeze at five years 0.7 per increase in log transformed BPA)[36] ; each 10% increase in exposure to dichlorodiphenyldichloroethylene (a product of the the pesticide DDT) was associated with increased wheeze at 12-14 months of age (RR 1.11)[143]; each unit increase in in utero electromagnetic exposure was linked with increased risk for asthma at 13 years (HR 1.15) [144].

DISCUSSION

The aim of this systematic review was to provide an overview of the literature describing associations between environmental exposures in early life and asthma outcomes by nine years of age. This review is mostly based on observational studies and is likely to be influenced by submission bias (where investigators do not submit papers which find no associations or challenges to current paradigms) and/or publication bias. In addition, reverse causation or confounding may explain some associations reported, e.g. postnatal exposures to antibiotics, paracetamol and perhaps pets. Moreover, observational studies cannot prove causation and most intervention studies found no effect on outcome even where studies indicated a potentially important mechanism, e.g. HDM interventions. Given these caveats, we believe that three major conclusions can be drawn. First, there was a moderately strong level of evidence (i.e. RCT, systematic review or

meta analysis) for the presence of associations between most exposures and asthma risk but the literature remains relatively deficient for exposures to infection and domestic combustion (both of which are likely to be important on a global basis). Second, where associations were present, these were of small-moderate effect size by our predefined standard. Third, we identified interactions between exposures (most commonly second hand smoke) and/or atopy which increased the risk of that exposure being associated with asthma. Given that there is no prospect of a cure for asthma, modification of the environment in early life currently offers the best hope of reducing the burden of asthma in the population and an overview of all exposures such as we present here may be of use to policy makers, health care workers and lobbying groups.

There is no single exposure which seems likely to cause asthma and even "single" exposures are invariably contaminated by other exposures. There was consistent evidence in the literature for associations between exposures to SHS, inhaled chemicals, mould, respiratory viruses, ambient air pollutants and maternal dietary components and increased asthma risk. However, each of these is a complex exposure and there was evidence of interaction between all these exposures. There is evidence that asthma risk may be related to diversity of exposure to fungus and not exposure *per se*[145] and our findings are consistent with this idea. There were inconsistent associations between asthma and exposures to pets, breast feeding and infant diet when considered separately but those intervention studies where asthma risk was successfully reduced often included modifications to some or all of these exposures. This is further evidence that asthma risk can be reduced by early exposure to an environment which is diverse in many inhaled and ingested factors common to the human environment for millennia, such as animal dander, LPS, fungi and breast milk (but not including man-made chemicals) although the exact nature of the exposure may not be relevant.

There are a number of limitations to this systematic review in addition to those already described. Firstly, in the absence of a gold standard definition of asthma, different outcomes have been used,

e.g. asthma or wheeze; these may not be interchangeable and have different associations with a given exposure. Secondly, associations reported may not be persistent: exposure to breast feeding is an example of a waning effect of a given exposure over time, presumably as current exposures modify the effect of past exposures. Thirdly, the upper age of study participants was nine years and this meant that many highly cited studies describing associations between exposure and asthma risk were not included[146]. Finally, it is possible that different exposures may have a different effect on asthma risk between populations where different genetic and/or epigenetic factors may be acting.

In summary, we have reviewed the literature for all environmental exposures on asthma causation in children aged under nine years. Early life exposures to exhaled tobacco smoke, volatile organic compounds, breastfeeding, pets and many dietary factors appear to be important to asthma causation and interactions between these exposures further increase this risk, particularly in individuals with allergic parents. Complex interventions in early life are challenging[147] but the evidence in the observational literature and from small intervention studies demonstrate that approaches using this study design may lead to stronger public health advice that such interventions are able to modify asthma risk in this age group.

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FIGURE LEGEND

Figure 1: QUOROM Statement Flow Chart.

Table I: Areas for environmental determinants of causation and exacerbation of asthma derived from stakeholder workshop.

Environmental tobacco smoke (antenatal and postnatal)
Domestic combustion (cooking, heating and candles)
Inhaled chemicals (Volatile Organic Compounds (VOC's), Chlorine, phthalates, Sulphur dioxide, Ozone)
Damp housing/ mould
Inhaled allergens (house dust mite, pets, pollens)
Air pollution
Dietary exposures (Maternal diet, breastfeeding, diet in childhood)
Respiratory virus infection
Medications (antibiotics and paracetamol)
Industrial combustion (incinerators)
Fireworks and bonfires
Vacuuming
Air conditioning or humidifiers

Table 2. Magnitude of effect of environmental exposure on respiratory symptoms including wheeze (*), asthma (†), obstructive bronchitis (¶) or atopic disease (¥) in children aged up to nine years. Details of when the exposure occurred are presented in the text and the supplemental table. ‡ indicates a randomised clinical trial, systematic review or meta analysis

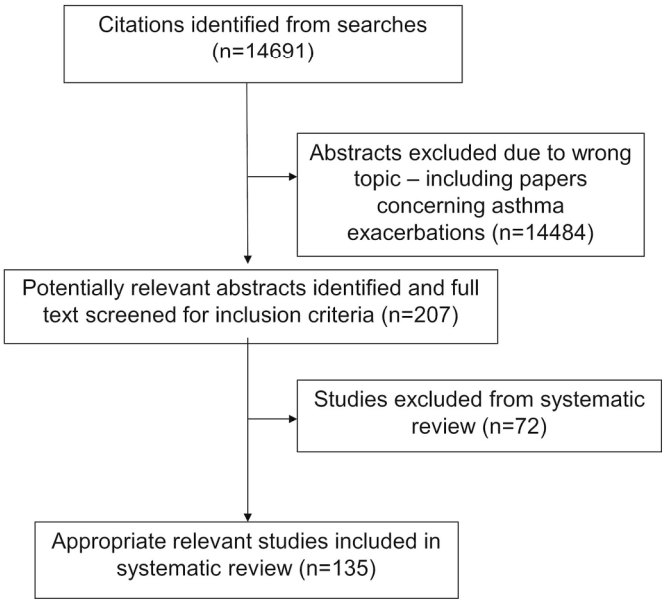
Exposure		Magnitude of effect [95 % confidence interval]
Second hand smoke	Antenatal exposure	1.7 [1.2, 2.3]‡[12] 1.13 [1.04, 1.23]* [13] 2.1 [1.2, 3.7]†[14] 1.35 [1.13, 1.62]†[15] 4.0 [1.9, 8.6]*[16] No association[17]
	Post natal exposure	1.3 [1.1, 1.6] †‡[5] 1.2 [1.0, 1.3] *[18] 2.9 [1.1, 7.2] *[17] 1.7 [1.1, 2.58]†[19]
Domestic combustion	Gas cooking	No association [21]
	Fine particulates ($PM_{2.5}$)	1.5 [1.1, 2.2] per quartile $PM_{2.5}$increase*[22]
	Detectable Sulphur Dioxide	OR 1.8 [1.1, 3.1]*[23]
	Incense	No association[24]17 [23]
	Biomass	4.3 [3.0, 5.0] † [25]
Inhaled Chemicals	VOC	1.2 [1.01, 1.4] per 10µg/m^3 increase†[26] 4.2 [1.4, 12.9]¶ [27] 2.1 [1.1, 3.9] per microg/m^3 of total MVOC *[28] 1.39 [no CI given]† [29] 2.92 [2.25, 3.75] †[30]
	Petrochemical plant	2.76 [1.96, 3.89] †Wichmann
	Chlorinated swimming pools	0.5 [0.3-0.9]†[31] No association ¥ [32]
	Other chemicals	1.7 [1.2, 2.4]* [34]33 (cleaning agents)
		1.6 [1.2, 2.1]†‡[33] (PVC)
		1.9 [1.1, 3.2]†[35](pyrene)
		0.7 [0.5, 0.9]*[36] (maternal BPA)
		1.4 [1.0, 1.9]*[36] (child BPA)
		2.8 [2.0, 3.9]†[37]and 1.7 [1.01, 2.9]*[38] (oil refinery)
Damp housing/mould		1.5 [1.3, 1.7]†‡[39] 1.4 [1.1, 1.8])*‡[40] (no association at 6-8 years) 7.1 [2.2, 12.6] †[41] 2.4 [1.1, 5.6] † [42] for exposure 2.6 [1.1, 6.3][43] per unit increase in mould index 1.8 [1.5, 22] [44] per unit increase in mould index
Multiple exposures		0.7 [0.5, 0.9]‡[48] 0.4 [0.3, 0.8]‡[49] 3.0 [1.1, 7.9] for high HDM† and 1.2 [1.1, 1.4]* per quartile LPS increase[50] 1.8 [1.02, 3.0]*increasing cockroach allergen[55] and 0.3 [0.1, 0.98]*for dog and 0.6 [0.4, 1.01]* for cat exposure[55] 2.6 [1.3, 5.4]† for high cat exposure[51] 2.7 [1.1, 7.1]† Dog and SHS, 4.8 [1.1, 21.5]† dog and elevated NO_2 [56]

		No association‡[45]‡ [46]‡ [47 52 53 54]
Inhaled allergens/particles	Pet	0.7 [0.6, 0.9])†‡cat exposure[59] 1.1 [1.0, 1.3])†‡dog exposure[59] 4.7 [1.2, 18.0])† cat exposure[61] 0.6 [0.4, 0.9]*cat exposure [62] 0.3 [0.1, 0.81]*cat exposure [63] 1.2 [1.1, 1.3]*cat exposure [64] No association‡[60 65 66]
	Other exposures	1.5 [1.1, 2.1]* highest vs lowest quartile LPS exposure [68] 1.4 [1.1, 1.7]*mouse allergen [69] 0.4 [0.2, 0.6]† feather quilt[70] 1.8 [1.0, 3.2]† number of synthetic bedding items [71] No association cockroach[52]
	HDM	No association‡[72]‡[73 74]
	Outdoor allergens	OR 3.1 [1.3, 7.4]*birthday during fungal spore season[75] OR 1.4 [1.1, 1.7]† grass pollen exposure[76] RR 1.2 [1.02-1.3]† tree canopy cover[77]
Air pollution		1.05 [1.00, 1.11]†‡ per ppm increased NO_2[78] 1.02 [1.00, 1.04]†‡ per ppm increased NO[78] 1.06 [1.01, 1.12]†‡ per ppm increased CO[78] 1.04 [1.01, 1.07]*‡ per ppm increased SO_2[78] 1.05 [1.04, 1.07]*‡ per unit increase particulates[78] 1.04 [1.01, 1.07]* per ppm increased CO[79] 1.2 [1.0, 1.31]† per 5ppb increase NO_2 [80] 2.0 [1.2, 3.6]† traffic related particles [82] 1.3 [1.0, 1.6]† higher traffic density [84] 3.1 [1.3, 7.4]† high exposure to $PM_{2.5}$ [85] No association[81]
Dietary exposures	Maternal dietary components during pregnancy	0.2 [0.08, 0.6]†‡ Mediterranean diet[86] 0.6 [0.4, 1.0]* Western diet[88] 0.6, [0.3, 0.96]* fish consumption[89] 0.8 [0.7-1.0]peanuts and 0.8 [0.7-0.8] tree nuts†[90] 1.6 [1.2, 2.0]low vegetables 1.5 [1.2, 1.8] low fruit and chocolate 1.4 [1.1, 1.7]†[91] No association fish oil[87]‡, butter and margarine[92]
	Specific nutrient intake during pregnancy	0.6 [0.4, 0.7]*‡ increased vitamin D intake[86] 0.7 [0.5, 0.9] *‡ increased vitamin E intake[86] 0.3 [0.1, 0.4] *‡ increased plasma vitamin A[86] 0.95 [0.91, 0.99]*per 10 nmol/L increase cord Vitamin D[97] No association vitamin D (plasma)[93-95] (intake)[96], dietary antioxidants[99] or folate[100] or vitamin A[101] supplements
	Breast feeding	OR 0.92 [0.86, 0.98]*‡[102] OR 1.1 [1.0, 1.2]†‡[102] 1.4 [1.2, 1.7]* never breast feeding [10302] 0.9 [0.8, 0.96]†exclusive breast feeding [104] 2.0 [1.0, 3.8]†maternal margarine intake during lactation [98] No association‡[105]
	Cows milk formula	RR 0.4, [0.2, 0.9]*‡hydrolysed vs standard[106] OR 0.3 [0.1, 1.0]*fatty acid supplementation [108] No association [109]
	Infant diet	0.4 [0.2, 0.9] for youngest vs oldest age at introduction of

		wheat †[111] 0.6 [0.4, 0.9] for early vs delayed introduction of fish[115] No association with age at introduction of solids[112,113] prebiotic supplementation‡[117]‡[118]or vitamin supplementation[119]
	Child diet	0.6 [0.4, 0.9]† full cream milk[121] 1.5 [1.04, 2.1] Western diet[124] 0.93 [0.85, 1.00] per fruit item consumption/day/week [125] 0.5 [0.3, 0.6] for highest vs lowest tertile plasma vitamin D[126] No association milk supplementation‡[120], organic food[122], dietary anti oxidant[123]
Respiratory virus infection	Respiratory infection±wheeze	0.5 [0.3, 0.9]† for infant lower respiratory tract infection [127] 9.8 [4.3, 22.0]*wheeze with rhinovirus[128] 2.9 [1.2, 7.1]†wheeze with rhinovirus [129] 2.2 [1.5-3.3]† RSV infection 6-11 months previously[130] 0.9 [0.7, 1.0]†early day care[132] No association early day care[131]
Medications	Antibiotics	1.2 [1.0, 1.5]†‡ antenatal exposure[135] 1.5 [1.3, 1.8]†‡ postnatal exposure[135] No association †‡[136]
	Paracetamol	1.3 [1.1, 1.4]†‡ [139] 1.2 [1.0, 1.4]*‡[138] No association[140]
	Other medications	1.1 [1.0,1.2] for antibiotics, 1.3 [1.1,1.6] gastroesophageal reflux treatment, 1.6 [1.1, 2.3] opiates, 1.3 [1.2, 1.4] thyroid supplements[140]
Other maternal exposures during pregnancy		2.7 [1.2, 6.0]* dietary dioxins and polychlorinated biphenyl[141] 2.3 [1.3, 4.1]* highest vs lowest BPA exposure[142] 0.7 [0.5, 0.9]* BPA exposure [36] 1.1 [1.0 1.2]* per 10% increase in DDT metabolite[143] 1.2 [1.0, 1.3] for increasing electromagnetic exposure[144]

Study	Interaction between	Magnitude of interaction
Robison[16]	Late premature delivery (<37 weeks) and antenatal SHS exposure	OR for wheeze 2.0 [1.3, 3.1] associated with prematurity and 1.1 [0.5, 2.4] with in utero SHS exposure. OR for wheeze 3.8 [1.8, 8.0] if both premature and SHS exposed
Martinez[19]	Smoke exposure from mother OR 1.7 [1.1, 2.6] for asthma by five years	OR 2.6 [1.4, 4.6] if exposed and mother ≤12 years education
Diez[27]	Redecoration Pet exposure Dampness	Redecoration associated with OR for obstructive bronchiolitis at 2 years 4.1 [1.4, 12.9]. OR 5.1 [1.6, 15.6] if also exposed to ETS or pets
Jung[35]	Pyrene exposure Atopy	High exposure was associated with increased risk for asthma 1.9 [1.1, 3.2] and this was increased to 2.9 [1.8, 5.7] among non atopic children
Carlsten[56]	Dog exposure SHS High NO_2	No association with dog exposure *per se*. OR 2.7 [1.1, 7.1] for dog and SHS. OR 4.8 [1.1, 21.5] for dog plus high NO_2
Karmus[57]	Recurrent lower respiratory tract infection SHS	OR 2.5 [1.8, 3.4] for asthma at ages 4 and 10 years. OR 3.1 [1.8, 5.2] with antenatal exposure to products of tobacco smoke
Melen[61]	Smoke exposure Pets Window pane condensation	OR for 1, 2 and 3 exposures (compared to none) were 1.1, 4.4 [1.0, 18.6] and 10.8 [2.0, 59.6].
Celedon 2002[62]	Early cat exposure Maternal asthma	Exposure associated with reduced risk for wheeze (OR 0.6 [0.4, 0.9]) but only in those with no maternal asthma.
Trevillian[71]	Synthetic bedding Bedroom heating Recent bedroom painting	Exposure to >1 synthetic item of bedding was associated with increased asthma (OR 1.8 [1.0, 3.2]). Co exposure to room heating was associated with OR 7.1 [0.1, 23.9], recent painting OR 7.2 [2.3, 23.2].
Kim [81]	Ambient air pollution (ozone, CO, NO_2, SO_2 and PM_{10}) Previous bronchiolitis	Asthma at five years not associated with higher exposures but among bronchiolitis subset ozone exposure associated with OR 7.5 [2.7, 21.3], CO exposure OR 8.3 [2.9, 23.7], and NO_2 exposure OR 7.9 [0.97, 64.8]).
Ryan [82]	Traffic related particles (elemental carbon attributable to traffic) Domestic LPS	A positive asthma predictive index at 36 months was associated with exposure to increased levels of particles before 12 months (OR= 2.0 [1.2, 3.6]). Co- exposure to high concentrations of endotoxin increased the risk (OR=3.4 [1.3, 8.9]).
Kusel[129]	Atopy Virus positive wheezing illness	OR 3.1 [1.5, 6.4] if atopic for wheeze at 5 years. OR 3.9 [1.4, 10.5] if also wheezy illness

Table 3. Magnitude of effect of main effect on asthma aetiology and magnitude of interaction with other factor.



QUOROM Statement Flow Chart.
190x142mm (300 x 300 DPI)

Supplementary file

Table I Characteristics of included studies

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Second hand Smoke-antenatal					
Neuman A, et al [1] (2012) Europe (UK, Spain, Sweden, Denmark, Germany, Netherlands)	Meta-analysis	21,600 children included in the analysis of which 735 (3.4%) met the criteria	To assess the effect of exposure to maternal smoking only during pregnancy on wheeze and asthma	A pooled analysis was performed based on individual participant data from eight European birth cohorts. Cohort specific effects were estimated using logistic regression and combined using a random effects model.	Maternal smoking during pregnancy was associated with increased risk of parental reported wheeze in the past 12 months and asthma (at least two out of three of the following criteria: (*1*) a doctor's diagnosis of asthma ever, (*2*) parental-reported wheezing during the last 12 months according to the ISAAC core questions or (*3*) asthma medication in the last 12 months) at 4 and 6 years - OR 1.4 [1.1, 1.8] and 1.7 [1.2, 2.3] respectively.
Jedrychowski et al. [2] (2009) Poland2009	Longitudinal	Children (n= 505, 468 responses) followed to the age of 2 years	To establish the pattern of prenatal environmental risk factors (ETS and particulate matter) related to the onset of wheezing phenotypes and severity of respiratory illness in early childhood.	Health and sociodemographic data collected from pregnant mothers . Children were followed up every three months to gather data on their respiratory symptoms and exposure to ETS.	Prenatal ETS exposure was associated with increased risk of wheeze (RR 1.1 [1.04, 1.23]. Other risk factors identified were maternal atopy and an inverse association with length of baby at birth.
Lannero et al.	Longitudinal	Children (n=4089,	To assess the possible	Data were collected for	Maternal smoking during pregnancy: positively

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
[3] (2006) Sweden	study	3791 total respondents) followed from birth to two years of age	effects of exposure to cigarette smoke in utero on lower respiratory disease in children up to two years of age.	maternal smoking during pregnancy, breastfeeding, parental smoking after birth, health of parents and any wheezing, recurrent wheezing and doctor diagnosed asthma in the children.	associated with asthma (OR 2.1 [1.2-3.7]).
Jaakkola et al. [4] (2004) Finland	Longitudinal	58841 (56632 total respondents) children followed for 7 years	To examine the relationship among maternal smoking in pregnancy and development of asthma in childhood.	Data collected for child's health and maternal smoking during pregnancy.	Maternal smoking during pregnancy: positively associated with risk of asthma in first seven years (OR 1.4 [1.1, 1.6]). Asthma was defined on the basis of at least 1 hospitalization due to asthma , at least 1 entitlement to free medication due to asthma or at least 1 entitlement to special care support due to asthma before the age of 7 years
Robison et al [5] (2012) USA	Longitudinal	1794 (1448 respondents) children	To investigate the interplay between exposure to tobacco smoke and prematurity in the aetiology of wheeze	Details of exposure to tobacco smoke and gestation at birth were gathered by questionnaire. Children were followed for a mean of 3.1 years and details about recurrent wheeze (≥ 4 episodes documented by physician)	Children with recurrent wheeze were more likely to have been born prematurely (average gestational age 36.5 ± 5.0 vs 37.7 ± 3.5 $p < 0.001$). There was no significant association between tobacco exposure, either in utero (OR 1.1 [0.5, 2.4]) or post natally (OR 1.4 [0.7, 2.7]). However, tobacco smoke exposure in combination with prematurity was associated with significantly increased risk of wheeze (OR 4.0 [1.9, 8.6]).

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
				obtained.	
Second hand Smoke-postnatal					
Vork et al. [6] (2007) USA	Systematic review	38 studies including approximately 200,000 children	To review the literature on second hand tobacco smoke and development of asthma in childhood	Defined asthma as wheezy bronchitis or asthma/wheeze that was ever doctor diagnosed or by a set of symptoms that are recognized criteria for diagnosing asthma in addition to wheezing	Results showed a positive association between exposure to tobacco smoke and development of asthma (RR 1.3 [1.1, 1.6]) in children 6-18 years of age.
Haberg et al. [7] (2007) Norway	Longitudinal	22390 children from fetal life to 18months	To assess children's exposure to parental cigarette smoke during and after pregnancy as risk factors for wheeze.	Data collected from parents and children on factors such as general health, nutritional status, socioeconomic status and environmental exposures. .	Maternal smoking: independent risk factor for wheeze (RR 1.25 [1.03-1.29]) Postnatal paternal smoking: risk factor for wheeze independent of maternal smoking (RR 1.14 [1.04-1.24]).
Tanaka et al. [8] (2008) Japan	Longitudinal	763 children followed through pregnancy until 24 months of age	To examine the association between maternal smoking during pregnancy and postnatal exposure to ETS and development of wheeze and asthma	Data collected for age, education, income, history of asthma, eczema and pre and post natal smoking history, wheeze and doctor-diagnosed asthma in the child.	Post natal maternal smoking, but not smoking in pregnancy, was associated with increased risk of wheeze in children (OR 2.9 [1.1, 7.2]). There was no association between smoking in pregnancy and development of wheeze or asthma.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Martinez et al. [9] (1992) USA	Longitudinal	786 children enrolled before 5 years of age	To determine the relationship of parental smoking at enrolment to subsequent incidence of asthma and lung function in a random sample of children.	Data collected from parents on smoking habits, history of wheeze or chronic cough, maternal education and data on asthma in children and lung function measurement.	Children of lower socioeconomic status were at increased risk of physician diagnosed asthma if their mothers smoked (RR 2.6 [1.4-4.6]).
Hunt et al [10] (2011) USA	Longitudinal	103 infants of asthmatic mothers	To evaluate the likelihood of infant wheeze in children exposed to varying levels of tobacco smoke and inhaled particulate matter	Particulate matter concentrations were recorded in each household. Urinary cotinine was measured 3 monthly for each infant to determine exposure to tobacco smoke. Infants were followed up for 1 year and data gathered on any diagnosis of wheeze.	Levels of particulate matter > 15 $\mu g/m^3$ were associated with increased risk of wheeze (OR 4.2 [1.4, 13.0]) Elevated urinary cotinine was also associated with a borderline increased likelihood of wheeze (OR 5.1 [0.96, 27.2])
Domestic combustion (solid fuel, gas and candles)					
Willers et al. [11] (2006) Netherlands	Longitudinal	Birth cohort (n=3148)	To investigate effect of kitchen ventilation while cooking on the relationship between gas cooking, combustion product dispersal and	Data collected for respiratory and allergic symptoms. Data was collected on gas cooking and kitchen ventilation.	Gas cooking was associated with nasal symptoms in four year olds but not with wheeze or asthma.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			respiratory outcomes in children.		
Jung et al [12] (2012) USA	Longitudinal	Children aged 5-7 (n = 262)	To evaluate the relationship between exposure to urban fine particulate matter and soot-black carbon and new onset wheeze	Integrated residential measurement of fine particulate matter and soot-black carbon was undertaken for 2 weeks in summer and 2 weeks in winter. Children were followed up for a 3 year period	Significant association was found between exposure to fine particulate matter ($PM_{2.5}$) and development of wheeze (RR 1.5 [1.05, 2.2] per quartile increase in exposure). Association was also seen between soot-black carbon exposure and development of wheeze but this was not significant (RR 1.4 [0.96, 2.1])
Yeatts et al [13] (2012) UAE	Cross sectional	628 households including 253 children and 330 adolescents	To evaluate the possible link between health problems including wheezing and asthma and exposure to indoor air pollutants	Passive air samplers were used to detect indoor air pollutants over a 7 day period. Health information was gathered by interview.	Participants in households with detectable SO_2, NO_2, and H_2S were twice as likely to report doctor-diagnosed asthma. Participants in homes with detectable SO_2 were more likely to report wheezing (OR 1.8 [1.05, 3.1]) and speech-limiting wheeze (OR 3.5 [1.06, 11.7]). $NO_2$and H_2S were also associated with increased risk for wheeze.
Padhi et al [14] (2008), India.	Case-Control	Children (1505) 5-10 years old living in 750 households (cases n=755; control n=750))	To determine the association between household use of biomass fuel for cooking and prevalence of asthma.	Questionnaire data collected for respiratory symptoms, household characteristics. Lung function measurements carried out.	Exposure to cooking smoke was significantly associated with doctor diagnosed asthma (OR 4.3 [3.0, 5.0]).

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Abdul Wahab et al [15] (2007), Qatar.	Case-control	Cases (n=100) mean age 4.31 SD 3.48, controls (n=100) mean age 4.37 SD 3.65	To determine whether exposure to environmental incense may contribute to the occurrence of asthma in Qatari children.	Data collected on past exposure to Arabian incense, family history of asthma, allergic rhinitis, atopic eczema and diagnosis of asthma.	Children exposed to incense were no more likely to have asthma (OR 0.9 [0.6, 1.2]).
Inhaled chemicals					
VOCs					
McGwin et al[16] (2011) USA	Meta analysis	7 studies	To review the possible link between formaldehyde exposure and childhood asthma	Data were extracted from the studies found and pooled in a meta analysis	Increase in formaldehyde exposure of 10µg/m^3 was associated with increased prevalence of asthma (OR 1.17 [1.01, 1.36), however definitions of asthma varied between studies.
Diez et al. [17] (2003) Germany	Longitudinal	Children (n=186) followed to 2 years of age.	To study the influence of redecoration on the occurrence of obstructive bronchitis in one and two year old children.	Data were collected at birth and at age 1 and 2 of the child. Information was gathered for redecoration of the apartments during pregnancy and first two years of life, smoking and presence of pet.	Redecoration of the home was positively associated with obstructive bronchitis (at two years OR 4.2 [1.4, 12.9]). Synergistic effects were seen with exposures to ETS and pets (OR 5.1 [1.6, 15.6]).
Kim et al. [18] (2007)	Cross sectional	1014 children from primary schools, median age 9	To study association between moulds, bacteria, MVOC (volatile	Data was collected on construction materials and ventilation. Samples were	MVOC and plasticizer concentrations were correlated r=0.5, p<0.01. MVOC and plasticizers were associated with an increased risk for any asthma (mean increased

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Sweden		(range 5-14, SD 2.0)	organic compounds of microbial origin), formaldehyde and selected plasticizer compounds in relation to doctor diagnosed asthma.	obtained to detect MVOC's, plasticizers and formaldehyde.	risk for asthma 2.1 [1.1, 3.9] per microg/m^3 increase in MVOC.
Rumchev et al. [19] (2002) Australia; Rumchev et al. [20] (2004) Australia	Case-control	Children 6months-3 years old, cases n=88, controls n=104 Cases were children diagnosed with asthma.	To determine whether early exposure to higher levels of indoor pollutants especially formaldehyde predisposes children to asthma.	Information collected for respiratory symptoms, skin prick tests carried out, formaldehyde levels estimated within the child's bedroom and living room.	Greater formaldehyde exposure during summer months. Those exposed to levels ≥ 60 µg/m^3 had an increased risk of asthma (OR 1.39, confidence intervals not provided). Cases were exposed to significantly higher levels of VOCs ($p<0.01$) especially benzene (OR 2.9 [2.25, 3.75]), ethyl benzene (OR 2.54 [1.16-5.56]) and toluene (OR 1.84 [1.41-2.41]).
Chlorine					
Font-Ribera et al. [21] (2011) Spain	Longitudinal	Children (n=5738) followed from birth to 7 years of age	To examine whether swimming in infancy and childhood was associated with asthma at age 7.	Data on swimming were gathered at regular intervals up to age 7 years. Other data gathered were information on wheezing, asthma asthma medication and potential confounders. Spirometry was carried out	Children with a high versus low cumulative swimming pool attendance from birth to 7 years had a reduced risk for ever (OR= 0.88 [0.56,1.38]) and current (OR 0.50 [0.28-0.87]) asthma.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
				from 7 to 8 years of age.	
Schoefer et al. [22] (2008) Germany	Longitudinal	Children (n=2192) followed from birth to 6 years of age	To assess whether early swimming pool attendance could be related to higher rates of asthma	Questionnaire data were gathered on socioeconomic status, medical history, lifestyle factors, information on first swimming pool attendance and doctor diagnosed asthma.	Early swimming pool attendance was not significantly associated with higher rates of atopic disease including asthma (OR 1.42 [0.65, 3.10]).
Henderson et al. [23] (2007) UK	Longitudinal	Children birth to 7 years of age (n=7162).	To assess effects of maternal use of domestic chemicals during pregnancy on wheezing and lung function.	Data collected for wheezing and household chemical exposure. Composite household chemical exposure (CHCE) score was determined.	Increased CHCE score was associated any reported wheezing: early (<18 months) OR 1.4 [1.1,1.8], intermediate (18-30 months) OR 1.4 [1.0,2.1] and late-onset (>30 months) OR 1.7 [1.2-2.4].
Other inhaled chemicals					
Jaakkola et al. [24] (2008) UK	Systematic Review	From the studies reviewed seven studies were in children age range 0-12 years of age	To review the evidence for the role of exposure to phthalates from PVC products in the development of asthma and allergies.	Seven studies in children consisted of cohort, cross sectional and case-control studies.	Presence of PVC materials in the homes: increased risk of asthma and allergy (OR 1.55 [1.2-2.1]), although definitions of asthma varied between studies
Jung et al [25]	Longitudinal	Dominican or African-American	To assess associations between exposure to	Personal air monitoring occurred for a 48 hour	High pyrene exposure was associated with increased incidence of asthma (OR 1.9 CI 1.13 – 3.2) There was

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(2012) USA		children (n= 354)	polycyclic aromatic hydrocarbons (pyrene and non-volatile PAHs) and development of asthma	period prenatally and for a 2 week period when the children were 5-6 years old; rates of diagnosis of asthma and use of asthma medication at 5-6 years of age were ascertained by questionnaire	no association between non-volatile PA H exposure and asthma
Donohue, KM et al[26] (2011) USA	Longitudinal Study	568 pregnant women followed up until children were 12 years of age	To determine whether BPA exposure is associated with increased risk of physician diagnosed asthma	Maternal spot urine samples were collected during the third trimester of pregnancy and from children at ages 3, 5 and 7. BPA urinary concentrations were measured.	Urinary BPA concentrations at ages 3, 5 and 7 were associated with increased odds of asthma. (OR, 1.5 [95% CI, 1.1-2.0], P = .005; OR, 1.4 [95% CI, 1.0-1.9], P = .03; and OR, 1.5 [95% CI, 1.0-2.1], P = .04 respectively. Prenatal urinary BPA concentrations were inversely associated with wheeze at 5 years.(OR 0.7 [0.5, 0.9] per
Wichmann et al. [27] (2009) Australia	Cross sectional	Children (n=1212) 6-12 years old	To determine the effects of exposure to petrochemical pollution on the respiratory health of the children.	Data on children's health collected using questionnaires, measurements carried out for particulate matter and volatile organic compounds.	Living near a petrochemical plant: increased risk of having a diagnosis of asthma (OR 2.76, 95% CI 1.96-3.89) and asthma exacerbations (OR 1.88, 95% CI 1.25-1.83).
Rusconi et al[28]	Case control	489 6-14 year olds	To compare the	Parents completed surveys	Weekly average concentrations of sulphur dioxide,

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
(2011) Sardinia			prevalence of asthma in an area polluted by an oil refinery with that in a non-polluted area	on the respiratory health and risk factors of their children. Concentrations of pollutants in each area were estimated. 12-14 year olds completed spirometry and levels of pollutants in nasal mucosa were also measured	nitrogen oxide and benzene were considerably higher in the area around the oil refinery than in the control area. Children living in the polluted area had higher levels of wheezing symptoms (PR 1.70 CI 1.01 - 2.86),decreased FEV_1 (-10.3%CI -15.0 - 6.0%) and FEF_{25-75} (-12.9% CI -20.7 -4.3%), increased FE_{NO} (+35% CI 11.7 - 80.1%) and increased in MDA-dG concentrations (83% CI 22.9% - 174.1%).
Damp housing, mould					
Tischer et al[29] (2011)	Systematic Review	61 observational studies included in the systematic review	To conduct a systematic review to investigate the association between domestic mould and mould components and asthma in children.	Data from 61 observational studies was included in this systematic review. Meta analyses of the effects of visible mould exposure on allergic health outcomes were performed and findings were evaluated according to the Bradford Hill criteria for evidence of causation.	Visible mould was positively associated with asthma (OR 1.49, 95% CI 1.28-1.72).
Tischer et al. [30] (2011)	Meta Analysis	Data from 8 European Birth cohorts	To investigate whether reported mould or dampness exposure in early life is associated with the development of	Data from 31742 children was analysed. Information on exposure to mould and dampness and health outcomes was available from	Exposure to visible mould and /or dampness during first two years of life was significantly associated with reported wheeze in meta analyses of four cohorts (0-2 years: OR 1.39, 95% CI 1.05-1.84) and associated with physician diagnosed asthma later in childhood in six

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			allergic disorders in children from eight European birth cohorts.	parental questionnaires.	birth cohorts (6-8 years: OR 1.09, 95% CI 0.90-1.32).
Iossifova et al.[31] (2009) USA	Longitudinal	Children (n=483) followed up to 3 years of age.	To examine how exposure to mould and (1-3)-β-D-glucan in infancy predicts the risk of future asthma.	Data were collected for home characteristics, Dust samples and tape samples were gathered. Infants were tested for allergen sensitization.	Presence of high visible mould (OR 7.1, 95% CI 2.2-12.6) and maternal smoking (OR 4.4, 95% CI 1.7-11.6) resulted in significantly higher scores on the Asthma Predictive Index, suggesting increased risk of developing asthma in future.
Jaakkola et al.[32] (2005) Finland	Longitudinal	Children (n=1984) 1-7 years old	To assess the independent and joint effects of parental atopy and exposure to moulds in homes and development of asthma.	Data on health indicators and exposure to mould (presence of odour, moisture, visible mould and water damage).	Presence of mould in the house: increased the risk of development of (doctor diagnosed) asthma (RR 2.44, 95% CI 1.07-5.60) independent of parental atopy.
Reponen et al[33] (2011) USA	Longitudinal	176 children followed up to age 7	To determine whether mould exposure at 1 or 7 years of age was associated with increased risk of asthma at age 7.	Household mould was assessed at 1 and 7 years using DNA analysis to calculate Environmental Relative Mouldiness Index (ERMI). Parents completed a questionnaire on asthma symptoms and children also	Children living in a high ERMI household at age 1 had an increased risk of asthma symptoms at the age of 7 compared to children living in low ERMI households at age 1 (OR 2.6 [1.1, 6.3]). However, living in a high ERMI household at age 7 was not associated with increased risk of asthma symptoms at age 7.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
				underwent spirometry.	
Reponen et al. [34] (2012) USA	Longitudinal study	289 children followed from birth to 7 years of age	To assess the relationship of early exposure to specific moulds on the development of childhood asthma.	Dust samples were gathered from homes of the children at 8 months of age and children were followed up at 7 years of age to collect data on lung function tests, diagnosis of asthma, home characteristics, exposure to cigarette smoke, skin prick tests and other demographic characteristics.	Asthma was diagnosed in 24% of children at age 7 years. Exposure during infancy to three mould species common to water damaged buildings was associated with childhood asthma at 7 years of age (RR 1.8 [1.5, 2.2]).
Indoor inhaled allergens – multiple exposures					
Marks et al. [35] (2006) Australia	Longitudinal study	Children (n=616) with family history of atopy followed to 5 years of age	To examine HDM avoidance and dietary fatty acid modification implemented throughout the first five years of life as interventions to prevent asthma	Children grouped into HDM avoidance and control and dietary modification or control. HDM avoidance was achieved through physical and chemical methods. Dietary modification constituted increasing proportion of long chain polyunsaturated fatty acids	There was no difference between the groups for onset of asthma.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
				in the diet.	
Arshad et al. [36] (2007) UK	RCT, longitudinal intervention study, Intervention period 1 year, children followed up to 8 years of age.	Children in high risk category (n=120, Intervention 58, Control 62)	To evaluate the effect of reduction in food and house dust mite allergen exposure in infancy in preventing asthma and allergy.	Intervention group infants were either breast fed with mother on low allergen diet or given hydrolyzed formula. Exposure to HDM was reduced by use of acaricide and mattress covers. Development of allergic diseases and sensitization assessed at ages 1, 2, 4 and 8 in all children.	Risk of asthma was significantly reduced in the intervention group during the first 8 years of life (OR 0.24, 95% CI 0.09-0.66, p=0.005).
Maas et al [37] (2011) Netherlands	RCT	443 children with a family history of allergic asthma	To determine whether an intervention aimed at reducing exposure to tobacco smoke, inhaled allergens and food allergens and increasing breastfeeding rates decreased rates of asthma in genetically susceptible children	Parents in the intervention group received an intervention aimed at reducing exposure to tobacco smoke and various allergens shortly before their child was born. Control group received standard care.	Although exposure to dust mites, dog and cat dander was reduced in the intervention group, there was no difference in prevalence of physician diagnosed allergic asthma at age 6 (OR 1.01 CI 0.58 – 1.76)
Dotterud et al. [38] (2013)	RCT	1374 (responders) women at first	To examine the impact of an intervention	Families in the intervention arm were given advice on	There was reduced parent reported asthma in the intervention group (OR 0.68 [0.52, 0.90]). The number

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Norway		ante-natal check-up (intervention; followed until 2 years post-natal) and 4780 women 2 years post-natal (group)	recommending increased consumption of n-3 PUFAs, decreased parental smoking and decreased household dampness on development of childhood asthma	increased n-3 PUFA consumption, smoking cessation and decreasing household dampness. n-3 PUFA consumption, smoking rates and household dampness were assessed at baseline and 2 years postnatally. Asthma rates in children were compared with rates in children of mothers not subject to these interventions.	needed to treat to benefit was 53. No reduction in wheeze between groups.
Chan-Yeung et al. [39] (2007) USA	RCT	545 children with at least one first degree family member with asthma. 469 assessed at 7 years	Antenatal and postnatal reduction of HDM, SHS and pets. Promotion of breast feeding and delayed weaning to solds	Pet exposure and maternal smoking was not changed by the intervention. Intervention was associated with reduced HDM, prolonged breast feeding and delayed weaning.	Risk for asthma reduced in intervention group (OR 0.44 [0.25, 0.79])
Celedon et al. [40] (2007) USA	Longitudinal	Children (n=440) followed from birth to 7 years of age	To examine the relation between exposure to dust mite allergen and endotoxin at age 2-3 months and asthma and	Data was collected on demographic and health indicators, environmental exposures, use of tobacco and samples were collected	Exposure to high levels of dust mite allergen (≥10µg/g) was associated with increased risk of physician-diagnosed asthma at 7 years of age (OR=3.0, 95% CI 1.1-7.9) Exposure to endotoxins in the highest quartile was associated with persistent wheeze (episodes at <3

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			wheeze in high risk children.	for dust from baby's bed and bedroom floor and family room.	and 6-7 years) (OR=3.5, 95% CI 1.3-9.8, p<0.05, p for trend <0.05).
Torrent et al. [41] (2007) UK and Spain	Longitudinal study	Children (n=1182) followed from before birth to 6 years of age.	To assess the role early life exposures to Der p1 and Fel d1 on the inception of sensitization and asthma.	Data was collected for details on pregnancy and samples were gathered for cord blood, dust, ambient NO2 and blood. Skin prick tests for mother and child. Yearly questionnaire data included details on respiratory symptoms, diagnosis, household environment, exposure to pets, tobacco smoke, cooking and heating appliances.	Exposure to Der p1 early in life was not related to asthma or persistent wheeze at 6 years of age. There was a significant association between cat allergen exposure and diagnosis of asthma OR=2.6, 95% CI 1.27-5.37.
Finn et al. [42] (2000) USA	Longitudinal	Children (n=114) followed from birth to 2 years of age.	To determine whether the levels of cockroach, house dust mite and cat allergen in the home during infancy were associated with allergen specific lymphocyte	Data collected for sociodemographic and health variables. Dust samples were collected at 3 months of age for various allergens. Blood samples obtained for allergen specific	No associations between exposures and wheeze at 2 years reported.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			proliferation in later life.	lymphocyte proliferation.	
Brussee et al. [43] (2005) Netherlands	Longitudinal	Children (n=1127) followed until 4 years of age	To investigate the effect of allergen exposure at 3 months of age on the development of sensitization, wheeze and physician diagnosed asthma in the first 4 years of life in a birth cohort of children with and without an atopic mother.	Data were collected for symptoms of wheeze, physician diagnosed asthma and samples were collected from child's mattress for exposure to HDM, cat and dog allergens.	A positive association was observed between exposure to cat allergen and persistent wheeze in total study population (OR=2.31, 95% CI 0.98-5.46, p<0.10) and exposure to dog allergen and persistent wheeze in children with a non atopic mother (OR=2.50, 95% 0.92-6.80, p<0.10).
Lau et al. [44] (2000) Germany	Longitudinal	939 children followed up to age 7 years	To assess the relevance of mite and cat allergen exposure for the development of asthma up to 7 years of age.	Newborns in the cohort followed up with data collected at various stages for food and inhalant allergens, indoor allergen exposure and interviews by paediatrician.	Sensitization to indoor allergens was associated with doctor diagnosed asthma, parents report of wheeze and increased bronchial responsiveness. However there was no relation between early exposure and prevalence of asthma or wheeze.
Litonjua et al. [45] (2002) USA	Longitudinal	Children (n=226) median age 2.87, range (1.10-4.99)	To investigate the longitudinal effects of exposure to house dust endotoxin (HDE), allergen levels and presence of dog in the home on	House dust samples were collected during infancy. Data were gathered for home characteristics, environmental exposures, demographic and socio-	When all were considered, increasing cockroach allergen exposure was positively associated with wheeze by age 5 years (1.8 [1.02, 3.0]) and presence of a dog and higher concentrations of cat allergen exposure were associated with reduced wheeze risk (OR 0.3 [0.1, 0.98] and 0.6 [0.4, 1.01]. In the

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			wheezing in young children over a 4 year period.	economic characteristics and wheeze in the past year for the participants.	multivariable model, exposure to LPS was not associated with wheeze at 5 but an association was present for wheeze at 2 years.
Carlsten et al. [46] (2010) Canada	Longitudinal Study	380 children recruited at birth, 184 assessed at 7 years of age	To evaluate the effect of combined early exposure to dog allergen and indoor nitrogen dioxide or environmental tobacco smoke on asthma and bronchial hyper reactivity in a high risk birth cohort.	Perinatal environmental tobacco smoke exposure was measured using cord blood cotinine. Data were also gathered for atopy, nitrogen dioxide and urinary cotinine in the first year. At 7 years of age children were assessed for asthma and bronchial hyper reactivity.	Coexposure to elevated dog allergen and nitrogen dioxide (OR 4.8, 95% CI 1.1-21.5) or dog allergen and environmental tobacco smoke (OR 2.7, 95% CI 1.1-7.1) increased the risk of physician diagnosed asthma relative to having neither such exposure.
Inhaled allergens - pets					
Lodge et al. [47] (2012)	Systematic review of longitudinal studies	9 longitudinal studies	To conduct a systematic review of longitudinal studies in urban environments to explore the relationship between cat and dog exposure in the perinatal period and subsequent asthma.	A qualitative synthesis of the nine studies was carried out. Data were extracted for a number of variables such as exposure variables, population type, family allergy history.	The findings suggest that for children without a family history of allergy, owning a dog was protective against the development of allergic disease. No overall effect size was presented
Takkouche et	Systematic	32 Studies	To examine the		Exposure to cats reduced the risk of physician

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
al. [48](2008) Spain	review		association between exposure to furry pets and asthma.		diagnosed asthma (RR 0.72, 95% CI 0.55-0.93). whilst exposure to dogs increased risk (RR 1.14m 95% CI 1.01-1.29)
Lodrup Carlsen et al. [49] (2012)	Meta-analysis	11 European Birth Cohorts children 6-10 year old	To examine the associations between pet keeping in early childhood and asthma in children aged 6-10 years.	Data from birth cohorts analysed for pet ownership and current asthma at 6-10 years of age	There was no association observed for furry and feathered pet keeping in early years of life and asthma (at least 2 of doctor-diagnosed asthma ever; asthma symptoms/wheezing in past 12 months (according to the International Study of Asthma and Allergy in Childhood); using asthma medication in past 12 months) in school age. Asthma comparing cat ownership with no pets (10 studies 11489 participants: OR 1.00, 95% CI 0.78-1.28) and dog ownership with no pets (9 studies 11433 participants: OR 0.77, 95% CI 0.58-1.03).
Melen et al [50] (2001) Sweden	Longitudinal	181 children aged 1-4 years (from cohort of 193)	To relate exposure to pets and other environmental factors at age 1-4 years to asthma outcomes	Dust collected and analysed for cat and dog allergen. Exposure to SHS and window pane condensation were ascertained from questionnaire	OR for 1, 2 and 3 exposures (cat allergen, SHS and window pane condensation, compared to none) were 1.11, 4.38 [1.03, 18.6] and 10.8 [1.97, 59.6].
Celedon et al. [51] (2002) USA	Longitudinal	Children (n=448) followed up to 5 years of age.	To examine the association between exposure to pets and asthma and wheezing in a	Questionnaire data was gathered for any pets in the house, history of wheezing or whistling in the chest.	Among children whose mother had no history of asthma, exposure to cat allergen of at least 8 µg/g at the age of 2-3 months was associated with a reduced risk of wheezing between 1-5 years of age (RR=0.6,

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			birth cohort of children whose mothers or fathers had a history of atopy.	Dust samples were collected from the household to test for cat and dog allergen.	95% CI 0.4-0.9). However this was not the case in children whose mothers had a history of asthma.
Perzanowski et al. [52] (2008) USA	Longitudinal	242 children followed up to 5 years of age (blood obtained in 323 at two yers)	To evaluate the relationship between cat ownership and development of early sensitization and wheeze.	Questionnaire data were gathered for sociodemographic and health indicators from birth to 5 years of age. Serum levels of anti- cat IgE and anti-Fel d IgG antibodies were measured.	Cat ownership was a risk factor for development of anti-cat IgE by 2years of age (RR 6.4, 95% CI 1.9-22) but not between years 2-5 (RR 0.88, 95% CI 0.24-2.3). Cat ownership was inversely related to current wheeze at 5 years (RR 0.26, 95% CI 0.083-0.81).
Brunekreef et al. [53] (2012) Netherlands	Longitudinal	206,332 children (aged 6–7 years))	To determine the relationship between cat or dog ownership and development of allergic symptoms	Parents answered questionnaires asking whether they had had a cat or dog in their home in the past year or during their first year of life. They were also asked questions regarding current symptoms allergic symptoms, including wheeze.	Cat ownership in the first year of life was associated with increased risk of current wheeze (OR 1.17 CI 1.09 – 1.26) and ever having wheezed (OR 1.12 CI 1.04 – 1.21) There was no significant association between current cat or dog ownership or dog ownership in the first year of life and wheeze.
Sandin et al. [54]	Longitudinal	Children (n=1228)	To assess the	Questionnaire data was	There was a positive but not significant association

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
(2004) Sweden		followed to 4 years of age	development of different wheezing phenotypes during the first 4 years of life in relation to heredity and early pet keeping.	collected for living environment, exposure to ETS, pets, family history of atopy, breast feeding, infectious diseases and antibiotics.	between wheezing and pet ownership and family history of atopy. However an inverse association was observed between pet ownership in the first year of life and risk of late onset wheezing at 4 years of age (dog keeping OR 0.4, 95% CI 0.2-1.0).
Kerkhof et al[55] (2009) Netherlands	Longitudinal	Children (n=2951) followed up to 8 years of age	To study prospectively the effects of pets at home on development of asthma from birth up to 8 years of age.	Data was collected on allergic symptoms in the child, pets at home and potential confounders during last trimester, at three months of age and yearly around the birthday of the child until 8 years of age.	A cat decreased the risk of HDM sensitization at age 8 , however there was no significant effect on incidence of asthma
Karmaus et al [56] (2008) UK	Longitudinal	Children (n=1456) followed up to 10 years of age	To characterize the joint effects of maternal smoking, breastfeeding for at least three months and recurrent lower respiratory tract infections on childhood asthma.	Data were collected after birth and at ages 1, 2, 4 and 10 years. Information was obtained from birth records and questionnaires on breastfeeding, respiratory infections, smoking history. Skin prick tests were carried out at age 4 and 10 years.	The three risk factors maternal smoking, breastfeeding for less than three months and recurrent lower respiratory tract infections together increased the risk of asthma at age 4 and 10 years (RR 3.1, 95% CI 1.84-5.23).

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Inhaled allergens – lipopolysaccharide/farm exposure					
Genuneit [57] (2012)	Systematic review with meta analysis	Systematic review of 39 studies, including 29 studies involving children	To determine the risk of exposure to farming environments and development of asthma and wheeze in rural populations	Results were described for childhood and adulthood studies.	Results for the childhood studies showed statistically significant combined estimates OR 0.75 indicating a 25% reduction in risk of developing asthma among exposed compared to the unexposed population.
Bolte et al. [58] (2003) Germany	Longitudinal (LISA)	Children (n=1942) followed until 2 years of age	To study the effect of early endotoxin exposure on incidence of atopic sensitization, atopic dermatitis and wheezing until the age of 2 years in infants with different risk status in terms of parental atopy.	Endotoxin measurements were obtained from mothers' mattresses. Data was collected on allergic symptoms, diagnoses of asthma and sensitization to common food and inhalant allergens was assessed by specific serum IgE.	Infants at risk due to parental atopy and exposed to high endotoxin levels had a 1.8 fold increased risk of repeated wheeze (OR 1.52, 95% CI 1.08-2.14 comparing highest and lowest exposure quartiles).
Phipatanakul et al. [59] (2008) USA	Longitudinal	Children (n=498) followed from birth to 7 years of age.	To examine the relationship between mouse allergen exposure and wheezing and asthma in first seven years of life.	Questionnaire data were gathered for home environment, atopy related symptoms, dust samples were collected from bedroom, baby's bed, kitchen and living room.	Current mouse exposure was associated with an increased risk of wheeze during the first seven years of life (OR 1.4, 95% CI 1.13-1.70, p=0.002)

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Nafstad et al. [60] (2002) Norway	Longitudinal	Children (n=2531) followed from birth to 4 years of age	To explore the association between early life exposure to feather bedding and risk of developing asthma in childhood.	Data were collected for respiratory symptoms at baseline and follow up contacts with the study subjects. Information was collected for type of quilt, family history of atopy, demographic details, exposure to ETS, breastfeeding, pets and lower respiratory tract infections in the first year of life.	Risk of developing physician diagnosed asthma at 4 years of age was lower in children using feather quilt at 6 months of age compared to those with a non feather quilt (OR 0.38 [0.23, 0.64].
Gehring et al[61] (2012) Netherlands	RCT	1282 children	To determine whether allergen-impermeable mattress covers reduced exposure to house dust mite (HDM) allergen and to assess whether reduced HDM allergen exposure resulted in a decrease in asthma	Children were prenatally randomised to receive allergen-impermeable or placebo mattress covers or no mattress cover. Parents completed yearly health questionnaires until the children were 8 years old. Allergen levels were	The HDM allergen Der-f1 was significantly reduced in the mattress dust from the allergen-impermeable group compared to placebo (geometric means ratio 0.31 CI 0.11 – 0.88). There was no difference between the placebo and no-cover groups. There was a decrease in asthmatic symptoms at 2 years old in the allergen-impermeable cover users compared to placebo. There was no significant difference between groups in asthmatic symptoms at 8 years. Raised levels

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			symptoms.	measured in the child's mattress dust. Specific IgE to a variety of allergens, including HDM allergens, was measured at 1 and 8 years.	of HDM allergen IgE were not associated with increased risk of asthmatic symptoms.
Indoor inhaled allergens – house dust mite					
Trevillian et al. [62] (2005) Australia	Longitudinal study (THIS)	Children (n=863)	To investigate the role of infant bedding items as part of a composite bedding environment in the development of childhood wheezing.	Data were collected on parent and infant characteristics, home environment, child care factors and infant sleeping environment at 1 month.	There was a dose response relationship between exposure to increasing levels of composite bedding in infancy and risk of wheezing (as reported by parents). OR for asthma by 7 years 1.8 [1.0, 3.2] comparing more synthetic bedding versus none.
Woodcock et al. [63] (2004) UK	RCT	291 infants of atopic parents (511 sets of parents screened) 239 followed up at 3 years of age.	To determine whether HDM eradication in pet free households before and after birth reduces risk for asthma	Stringent and effective HDM reduction measures introduced before delivery. Dust samples collected and analyses in the first month	The intervention arm were not at altered risk for wheeze at 3 years of age.
Carter et al. [64] (2003) USA	Longitudinal	Children (n=97) followed from birth to 7 year of age	To determine whether exposure to higher levels of dust mite in infants increased the risk of	During first two years of life monthly bedroom dust samples were collected. Between age 6 and 7 years	There was no significant association between HDM exposure and development of asthma, although those children who were sensitised to HDM were more likely to have asthma ($P < 0.05$).

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			bronchial hyper responsiveness or asthma by age 6-7 years.	data was gathered for diagnosis of asthma, skin prick test and methacholine inhalation challenge.	
Inhaled allergens - outdoors					
Harley et al. [65] (2009) USA	Longitudinal study	Children (n=514) followed from birth to 2 years of age	To examine whether birth during seasons of elevated ambient fungal spore or pollen concentrations is associated with risk of early wheezing or blood levels of Th1 and Th2 type cells at 24 months of age.	Early wheezing in children confirmed from medical records. Blood samples obtained to measure Th1 and Th2 type cells. Ambient aeroallergen concentrations measured during the study period.	Birth in autumn to winter was associated with increased risk of early wheezing (OR 3.1, 95% CI 1.3-7.4). Higher pollen concentration was associated with an increased risk of early wheeze. Being born during the spore season increased the risk of early wheezing.
Erbas et al. [66] (2012) Australia	Longitudinal study	620 children aged 6 or 7 years of age	To examine the to higher ambient levels of pollen in the first 3-6 months of life and risk of eczema, sensitization to food and aeroallergens at two years and asthma at age 6-7 years combined.	Data were gathered from birth using telephone surveys on development of allergic symptoms, skin prick tests were carried out and information on diagnosis of asthma	Cumulative exposure to pollen concentration between 4 to 6 months was associated with diagnosis of asthma (OR 1.35, 95% CI 1.07-1.72).

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Lovasi et al. [67] (2013) USA	Longitudinal study	727 children aged ≤ 7years	To investigate the association of tree canopy cover with subsequent development of asthma	Birth cohort data were linked with tree canopy coverage within 0.25km of the prenatal address. Other data gathered included response to specific allergens and information on diagnosis of asthma from parental report	Tree canopy coverage was positively associated with diagnosed asthma at 7 years (RR 1.17, 95% CI 1.02-1.33).
Air Pollution					
Gasana et al[68] (2012) USA	Meta-analysis	19 studies	To evaluate the link between exposure to traffic air pollutants and wheeze or asthma	Data from studies looking at exposure to traffic air pollutants and development of wheeze or asthma were extracted and pooled in a meta analysis	Exposure to nitrogen dioxide (OR 1.05 CI 1.00 – 1.11), nitrous oxide (OR 1.02 CI 1.00 – 1.04), and carbon monoxide (OR 1.06 CI 1.01 – 1.12) were associated with higher prevalence of diagnosis of childhood asthma. Exposure to sulphur dioxide (OR 1.04 CI 1.01 – 1.07) and particulate matter (OR 1.05 CI 1.04 – 1.07) was associated with a higher prevalence of wheeze in children.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Rodriguez et al. [69] (2007) Australia	Longitudinal	Children (n=263) from birth to 5 years of age	To examine the relationship between exposure to outdoor pollution and symptoms associated with respiratory illness.	Data collected on respiratory symptoms, air pollution indicators	Of the air pollutants studied (Ozone, CO, NO2 and PM2.5) only CO was associated with increased parentally reported wheeze (increased risk 1.035 [95% CI 1.005, 1.066] per ppm increase.
Nishimura et al [70] (2013) USA, Puerto Rico	Longitudinal	Latino (n=3343) and African-American (n= 977) children	To investigate the effect of exposure to high levels of air pollution in the first year of life on asthma development	Residential history and local air quality data used to calculate early life exposure to air pollution.	A 5 part per billion increase in nitrogen dioxide was associated with a increase risk of physician-diagnosed asthma (RR 1.17, CI 1.04-1.31)
Kim et al. [71] (2013) Korea	Longitudinal study	1743 children mean age 6.8 years	To investigate the effect of air pollution on the development of asthma in children with past episodes of bronchiolitis.	Data available from the parental responses to the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires and allergy evaluations were conducted in the children. Recent exposure to air pollution was estimated using geographic information system.	NO association with exposure but both exposure and past episodes of bronchiolitis asthma risk was increased (ozone+bronchiolitis OR 7.5 [2.7, 21.3], CO+bronchiolitis OR 8.3 [2.9, 23.7], NO_2 OR 7.9 [0.97, 64.8])

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Ryan et al. [72] (2009) USA	Longitudinal	Children (n=624) followed to 36 months	To determine whether co exposure to traffic related particles and endotoxin has additive effect on persistent wheezing during childhood.	Air pollution measurements were obtained for exposure at home, day care centres and other places frequented by the children.	A positive asthma predictive index at 36 months was associated with exposure to increased levels of particles (elemental carbon attributable to traffic) before 12 months (OR= 2.0 [1.2, 3.6]). Co- exposure to high concentrations of endotoxin increased the risk (OR=3.4 [1.3, 8.9]).
Bernstein [73] (2012) USA	Longitudinal	700 children with at least 1 atopic parent	To evaluate the risk of developing asthma in children exposed to traffic pollution	Exposure to traffic pollution was estimated and children had an annual medical assessment until age 4	Wheezing without a cold was present in 23% of African American children exposures to stop/go traffic 14% to moving traffic and 11% to unexposed children. Proportions were 13%, 6% and5% for Caucasian children
Patel et al [74] (2011) USA	Longitudinal	593 children already enrolled in a birth cohort study	To evaluate the link between traffic density and respiratory health	Cohort were followed until age 10 with data collected on traffic density in their local area(s) and diagnosis of asthma	Children living in areas with higher traffic density were more likely to be diagnosed with asthma (OR 1.26 CI 1.01 - 1.57) Children living in a high traffic density area at age 1 were more likely to develop wheeze in later years
Carlsen et al[75] (2011) Canada	Longitudinal	184 children	To assess the risk of asthma and bronchial hyper-reactivity in children exposed to traffic-related air pollutants	Exposure to NO, NO_2, black carbon and particulate matter during birth year was estimated by land use regression. Children were followed until the age of 7 for diagnoses of asthma and	High (> 4.1µg/m^3) levels of particulate matter were associated with significant increase in asthma (OR 3.1 CI 1.3 - 7.4) and trends towards increased risk of bronchial hyper-reactivity. Similar findings were seen for NO and NO_2 but there was no increased risk seen with exposure to black carbon.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
				bronchial hyper-reactivity.	
Dietary exposures					
Maternal diet during pregnancy – food items					
Nurmatov et al. [76] (2010) UK	Systematic review	62 studies	To investigate the evidence that nutrient and food intake modifies the risk of children developing allergy.		Meta analysis of studies not possible, effect size not given. More convincing evidence for maternal fruit intake during pregnancy reducing asthma risk compared to vegetable intake. Evidence insufficient between Mediterranean diet and asthma risk. Fish exposure not included
Miyake et al. [77] (2011) Japan	Longitudinal	763 mother-child pairs	To examine the relationship between maternal dietary patterns during pregnancy and the risk of wheeze in the offspring aged 16-24months	Data on maternal dietary intake during pregnancy was assessed. Three dietary patterns were identified: 'healthy' with high intake of green and yellow vegetables, seaweed, mushrooms, white vegetables, pulses, potatoes, fish, sea products, fruit and shellfish; 'Western' included high intake of vegetable oil, salt-containing seasonings, beef and pork, processed meat, eggs, chicken and	Decreased maternal consumption of Western diet during pregnancy was associated with decreased risk of childhood wheeze. After adjustment for the confounding factors, ORs in the first, second, third, and fourth quartiles were 1 (reference), 0.72 (95% CI: 0.44–1.17), 0.52 (95% CI: 0.31–0.87), and 0.59 (95% CI: 0.35–0.98), respectively (p for trend = 0.02)

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
				white vegetables; 'Japanese' is high intake of rice, miso soup, sea products and fish. Symptoms of wheeze and were based on criteria from the International Study of Asthma and Allergies in Childhood	
Romieu et al. [78] (2007) Mexico	Longitudinal	462 pregnant women enrolled and children followed from birth to 6 years of age.	To evaluate the impact of fish oil consumption during pregnancy on the incidence of asthma.	Dietary intake of women assessed by using a food frequency questionnaire. Data gathered yearly on episodes of wheezing, diagnoses of asthma, serum samples gathered for specific IgE levels and skin prick tests were carried out..	Fish intake during pregnancy was protective against atopic wheeze at 6 years of age (OR 0.55, 95% CI 0.31-0.96). An increase of fish intake from once per week to 2.5 times per week decreased the risk of wheeze at age 6 years by 82%.
Maslova et al (2012) Denmark[79]	Longitudinal	61,908 mother-child pairs	To determine whether high levels of maternal tree nuts and peanuts during pregnancy were associated with increased	Maternal tree nut and peanut consumption was estimated using a validated questionnaire. Parental questionnaires were used to determine prevalence of	Maternal intake of peanuts (OR, 0.79; 95% CI, 0.65-0.97) and tree nuts (OR, 0.75; 95% CI, 0.67-0.84) was inversely associated with asthma in children at 18 months of age. Higher tree nut intake was inversely associated with a medication-related asthma diagnosis (OR, 0.81; 95% CI, 0.73-0.90). Compared with mothers

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			risk of childhood asthma.	recurrent wheeze (>3 episodes) and 18 months of age and diagnosed asthma at 7 years.	consuming no peanuts, children whose mothers reported eating peanuts 1 or more times per week were 0.66 (95% CI, 0.44-0.98) times as likely to have asthma.
Erkkola, M et al[80] (2012) Finland	Longitudinal study	2441 children at 5yrs of age	To study the effect of maternal food consumption during pregnancy on the emergence of asthma and wheeze by 5 yrs	Data from children were analysed within the Finnish Type 1 Diabetes Prediction and Prevention Nutrition Study. Maternal diet was assessed with a validated food frequency questionnaire	Low maternal consumption of leafy vegetables ([aOR]: 1.55; 95% CI: 1.21, 1.98), malaceous fruits (aOR: 1.45; 95% CI: 1.15, 1.84), and chocolate (aOR: 1.36; 95% CI: 1.09, 1.70) were positively associated with the risk of wheeze in children. No associations were observed between maternal food consumption and asthma.
Nwaru, BL et al [81] (2012) Finland	Longitudinal Study	2441 children	To investigate the effect of maternal intact of fatty acids during pregnancy on the risk of wheeze.	Information on maternal diet was assessed by a validated FFQ and information on allergies was analysed by the International Study of Asthma and Allergies in Childhood	There was no significant association between maternal consumption of fatty acids during pregnancy and childhood wheeze.
Maternal diet during pregnancy – individual nutrients					
Nurmatov et al. [76] (2010) UK	Systematic review	62 studies	To investigate the evidence that nutrient and food intake modifies		Serum vitamin A was lower in children with asthma compared to controls (OR 0.25, 95% CI 0.10-0.40). High maternal dietary vitamin D and E intakes during

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			the risk of children developing allergy.		pregnancy was protective for development of wheeze (OR 0.56, 95% CI 0.42-0.73 and OR 0.68, 95% CI 0.52-0.88 respectively).
Dunstan et al. [82] (2003) Australia	RCT	83 pregnant mothers	To determine whether fish oil supplementation modified neonatal immune responses	Atopic mothers were randomised to placebo or fish oil supplement during pregnancy. Infants followed up at one year	No difference in respiratory outcomes between groups.
Pike, KC et al[83] (2012) UK	Longitudinal Study	860 pregnant women and their children up to 6 years	To assess the relationship between mother serum 25-hydroxyvitamin D status and asthma and wheeze phenotypes in their children at 6 years of age.	Data was collected in the 34th week of gestation and questionnaire data collated from 6, 12, 24 and 36 months and 6 years of age. Spirometery and skin prick testing was performed at 6 years of age.	There were no significant associations between late maternal 25-hydroxyvitamin D status and either asthma or wheeze at 6 years. No associations were found with either skin sensitization or lung function.
Morales, E et al [84] (2012) Spain (742)	Longitudinal Study	1724 children	Assessment of whether maternal circulation 25-hydroxyvitamin D (25[OH]D) concentrations in pregnancy were associated with a risk of wheezing and asthma in	Maternal circulating 23(OH) D concentrations were measured in pregnancy (mean gestational age = 12.6 weeks). From the age of 1 parents were asked annually if their child had a physician-confirmed history of LRTI or	There was a trend for an association between higher levels of circulating 25(OH)D in pregnancy and decreased odds of LRTI in offspring)(for cohort- and season-specific quartile Q4 vs. Q1, odds ratio = 0.67 [95% confidence interval = 0.50-0.90]; test for trend, P = 0.016) No association was found between 25(OH)D levels in pregnancy and risk of wheezing at 1 or 4

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			the offspring	wheezing. Asthma was defined as parental report of a doctor diagnosis of asthma or treatment at the age of 4-6 years	years, or asthma at age 4-6 years
Hollams, Em et al[85] (2011) Australia	Longitudinal Study	989 6 year olds and 1,380 14 year olds	To investigate associations between plasma vitamin D and allergy and asthma development in children age 6 and 14 years	Serum Vitamin D was assayed in the 6 and 14 year olds. Lung function was assessed by spirometry and BHR was assessed by metacholine challenge. Total and specific IgE were measured by ImmunoCap and subjects were considered atopic if they had any measured specific IgE ≥0.35 $kU \cdot L^{-1}$ for age 14 yearsor total IgE ≥100 $kU \cdot L^{-1}$ for age 6 years	Relationships between Vitamin D status and clinical conditions were seen only amongst males. Compared to those with sufficient Vitamin D, males without sufficient Vitamin D had an increased frequency of BHR (19.6 versus 13.3%; p=0.031) atopy (72.2versus 61.1%; p=0.003) and HDM sensitisation (50.2 versus 39.8%; p=0.007), The trends were similar or asthma (13.5 versus 9.4%; p=0.094) and poor lung function (12.5 versus 8.5%; p=0.087)
Miyake, Y et al[86] (2011) Japan	Longitudinal study	763 Japanese child-mother pairs	To investigate the relationship between maternal vitamin B intake during pregnancy and wheeze and eczema in infants ages 16-24	Data on maternal intake were assessed with a diet history questionnaire. Symptoms of wheeze were based on the criteria of the international study of	There were no significant relationships between maternal consumption of Vitamin B and folate during pregnancy and the risk of wheeze n the offspring.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			months	asthma and allergies in childhood.	
Camargo et al. [87] (2011) USA	Longitudinal	Children (n=922)	To examine the role of vitamin D in childhood respiratory health.	Cord blood levels of newborns were tested for 25 (OH) D. Details on any respiratory symptoms were collected at 3 months and 15 months and annually thereafter to 5 years of age.	Cord blood levels were inversely associated with risk of wheezing from age 3 months to the age 5 years (OR 0.95 [0.91, 0.99] for wheeze by 5 years per 10 nmol/L increase). Similar relationship was not identified for asthma.
Lumia et al[88] (2011) Finland	Longitudinal study	1798 children	To explore the association of maternal dietary FA composition during pregnancy with the risk of asthma in the offspring	Dietary intake was assessed by a food frequency questionnaire 8 months into the pregnancy and the occurrence of asthma assessed at 5 years with a modified questionnaire from the ISSAC	Low maternal intakes of α-linolenic acid [lowest quarter vs. mid-half HR 1.67 (95% CI 1.12–2.48)] and total n-3-polyunsaturated fatty acids [HR 1.66 (95% CI 1.11–2.48)] during pregnancy were associated with an increased risk of asthma in the offspring, while a low intake of arachidonic acid [HR 0.52 (95% CI 0.32–0.84)] and high intake of total saturated fatty acids [highest quarter vs. mid-half HR 0.55 (95% CI 0.34–0.90)] and palmitic acid [HR 0.51 (95% CI 0.31–0.83)] were associated with a decreased risk of asthma
Nwaru et al [89] (2011) Finland	Longitudinal Study	2441 children	To investigate the association between maternal intake of antioxidants during pregnancy and the risk of	The study was on the basis of the Finnish Type 1 Diabetes Prediction and Prevention Nutrition study, complete information on	Maternal intake of antioxidants was not significantly associated with the risk of asthma in offspring.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			asthma, rhinitis and eczema in 5 year old children	maternal food frequency questionnaire data and ISSAC- based allergic outcomes were available for 2441 children	
Martinussen et al. [90] (2011) Norway	Longitudinal	1,499 women – and their children who were followed up until the age of 6years	To assess whether maternal folic acid intake during the first trimester of pregnancy is related to asthma in the offspring by the age of 6 years	Data on folic acid use and content was collected before 24weeks of gestation, and at a month before conception through the third month of pregnancy. Asthma in the children was assessed at the age of 6years	Folic acid supplementation during pregnancy did not lead to a statistically significant decrease in asthma at 6 years of age.
Checkley, W et al[91] (2011) USA	Longitudinal Study	5,430	To examine the long term effects of Vitamin A supplementation early in life on later asthma risk	Two cohorts were enrolled in randomised Vitamin A supplementation. One cohort received Vitamin A or placebo for <16 months during their pre-school years. The second cohort was born to mothers who received Vitamin A before, during or after pregnancy. At follow-up both cohorts were asked about asthma	No difference was found between the Vitamin A supplemented and placebo groups from either trail in the prevalence of lifetime or current asthma and wheeze, [$p \geq 0.12$ for all comparisons]

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
				symptoms and spirometry was performed.	
Breastfeeding					
Brew et al (2011)[92]	Meta-analysis	31 studies	To investigate the link between any or exclusive breastfeeding and development of childhood wheeze or asthma.	Meta-analysis and subgroup analysis.	There was no association found between any or exclusive breast feeding and wheezing illness. Subgroup analysis found that breast feeding slightly lowered the odds of wheeze (pooled odds ratio 0.92 [0.86, 0.98]) but slightly increased the odds of asthma (pooled odds ratio 1.10 [1.00, 1.22]) when asthma was defined as the presence of any two of: ever diagnosed by a physician, wheeze in the last 12 months, use of asthma medication in the last 12 months and bronchial hyper-responsiveness).
Sonnenschein-van der Voort et al. [93] (2011) Netherlands	Longitudinal	5,369 preschool children	To examine the associations of breastfeeding duration and exclusiveness with the risks of asthma-related symptoms in preschool children – and to explore whether these associations are explained by atopic or	Information on breastfeeding duration and exclusiveness were obtained at 2, 6 and 12months after birth. Information on asthma-related symptoms was obtained at the ages of 1, 2, 3 and 4years.	Children who were never breastfed had increased risk of wheeze during the first 4 years of life (OR 1.44 CI 1.24 – 1.66) compared to children who were breastfed for 6 months. Children who were never breastfed, or breastfed for only 3 or 6 months tended to have asthma-related symptoms earlier than those who were breastfed for >6 months although these results did not reach statistical significance (HR 1.13 CI 0.97 – 1.32; HR 1.06 CI 0.96 – 1.17; HR 1.03 0.92–1.15).

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			infectious mechanisms		
Silvers et al. [94] (2012) New Zealand	Longitudinal	892 infants from birth to the age of 6 years	To investigate the effects of breastfeeding on wheezing and current asthma in children from 2 to 6 years of age	Breastfeeding in 1105 infants was assessed at birth and at 3, 6 and 15months-breastfeeding was assessed in two ways: 'exclusive' and 'any'. The infants were assessed for 'current asthma' or 'current wheezing' at 2, 3, 4, 5 and 6years	Exclusive breastfeeding was associated with decreased risk of asthma at 2 (OR 0.85 CI 0.76 - 0.94), 3 (OR 0.88 CI 0.80 - 0.97), 4 (OR 0.92 CI 0.84 – 1.0) and 5 years (OR 0.88 CI 0.80 - 0.96) but no significant decrease in risk of asthma at 6 years. Any breastfeeding was also associated with decreased risk of asthma at 2 (OR 0.94 CI 0.90 – 0.97), 3 (OR 0.94 CI 0.91 – 0.97), 4 (OR 0.96 CI 0.92 – 0.99) and 5 years (OR 0.98 CI 0.94 – 1.0) but no significant decrease in risk of asthma at 6 years.
Kramer et al [95] (2007) Belarussia	RCT	17046 pregnant mothers 13889 children followed up at 6.5 years	To determine whether prolonged breast feeding had a durable effect of asthma outcome	Mothers were randomised by centre to receive breast feeding promotion or standard advice	There was no difference between children who received the intervention and standard advice.
Lumia et al[96] (2012) Finland	Longitudinal Study	1798 mother-child pairs from the Type 1 Diabetes Prediction and Prevention Nutrition Study	To explore the association between maternal dietary fat and fatty acid intake during lactation and the risk of asthma in the offspring	Dietary intake was assessed by a food frequency questionnaire and the cumulative incidence of asthma assessed at 5 years with a modified questionnaire from the	The maternal use of margarines was associated with a marginally increased risk of asthma (hazard ratio (HR) for user vs. nonuser 1.96, 95% confidence interval (CI) 1.01–3.82, p = 0.047) The maternal intake of of FA and fish during lactation were not associated with the risk of asthma.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			by 5 years	ISSAC	
Infant feeding/weaning					
Ram et al [97] (2004) Netherlands	Systematic review	10 trials	To quantify the risk of asthma or wheezing in infants fed standard cow's milk based formula compared to hypoallergenic formulas.		Risk of wheezing and asthma was reduced in infants when using hydrolysed milk formulas in the first year of life. (RR 0.40, 95% CI 0.19 to 0.85) There was insufficient evidence to suggest benefits of soya based milk formula in modifying the risk of wheeze or asthma.
Morisset et al. [98] (2010) France	Randomised controlled trial	129 children from birth to the age of 24months	To determine the impact of the not-hydrolysed fermented infant formula 'HKBBST' on the incidence of allergy-like events during the first 2years of life in children at high risk of atopy	Infants were given either HKBBST (n=66) or standard infant formula (n=63), from birth until the age of 1year, and were followed at 4, 12 and 24months after birth. Skin prick tests for foods (cow's milk, hen's egg, codfish, wheat flour, soy flour and roasted peanut) and aeroallergens (dermatophagoïdes pteronyssinus, cat and dog dander, grass pollens, birch pollen and Alternariia alterna) were performed,	Use of HKBBST decreased respiratory potentially allergic adverse events(wheeze, wheezy bronchitis and spastic bronchitis) (7 vs 21%, P=0.03) at 12 months, at 24 months (13 vs 35%, P=0.01).

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
				and adverse events were recorded	
Birch et al. [99] (2010) USA	RCT	Children (n=89)	To assess the effects of Docosahexanoic acid (DHA) or Arachadonic Acid (ARA) supplementation in infancy, consistent with worldwide human milk levels on the incidence of respiratory infections and allergic illnesses through 3 years of age.	Infants were randomly assigned to receive either DHA or ARA formula. Data were gathered for episodes of allergic manifestations, respiratory illnesses during the first three years of life.	The DHA/ ARA group had significantly less chance of developing wheezing/ asthma (OR 0.32, 95% CI 0.11-0.97).
Kuo et al. [100] (2011) Taiwan	Longitudinal	679 infants who had at least 1 1st degree family member with a history of atopy. Followed from birth to the age of 36months	To investigate whether feeding a protein-hydrolysed formula (HF) in the first 6months of life decreased allergic diseases up to 36months later. This was compared to cow's milk (CM) consumption	Infants were fed with HF or CM for at least 6months via an open-label protocol, and were monitored prospectively at 6, 18 and 36months of age, to asses allergy sensitisation and allergic disease	Infants fed with HF during the first 6months of life had a no significantly reduced risk of asthma compared to CM fed infants.
Nwaru et al.	Longitudinal	3781 children from birth to the age of	To investigate the associations between the	Dietary exposures were analysed at the ages of 3, 6	Introduction of wheat, rye, oats, and barley before 5 months (OR 0.72 CI 0.44 - 1.19) or at 5 to 5 and a half

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[101] (2013) Finland		5years	duration of breast-feeding and timing of introduction of complementary foods and the development of asthma and allergies by the age of 5years	and 12 months. Further forms were filled regarding the age at which new food was introduced. The exposures of interest were: breastfeeding, cow's milk; roots (carrots, potatoes, turnips); fruits and berries; wheat, rye, oats and barley; meat; fish; eggs; and other cereals (maize, rice, millet and buckwheat)	months (OR 0.59 CI 0.41 - 0.86) was associated with decreased risk of asthma compared to introduction after 5 and a half months. Introduction of egg before 8 months (OR 0.61 CI 0.39 - 0.94) or at 8 to 11 months (OR 0.55 CI 0.38 - 0.81) was associated with decreased risk of asthma compared to introduction after 11 months.
Virtanen et al. [102] (2010) Finland	Longitudinal	Children (n=1293)	To assess how age at introduction of different foods or food groups as well as breastfeeding during the first year of life is related to the emergence of asthma and allergic rhinitis by the age of 5 years in a cohort of children with increased HLA-DQB1-conferred risk for type 1 diabetes.	Data on infant feeding patterns was gathered suing a dietary questionnaire. At 3,6,12 and 24 months of age. Data were also collected for history and symptoms of asthma, allergic rhinitis and atopic eczema at 5 years of age.	Early age at introduction of oats was associated with a reduced risk of persistent asthma for the first tertile (HR 0.36, 95% CI 0.15-0.85) and mid tertile (HR 0.37, 95% CI 0.22-0.62) compared to the last tertile ($p<0.001$). Similar results were also observed for introduction of fish ($p<0.001$).
Mihrshahi et	Longitudinal	Children (n=616)	To examine the	Information was provided on	No association between introduction of solids before 3

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al. [103] (2007) Australia	(CAPS Childhood Asthma Prevention Study)	followed up to 5 years of age	relationship between infant feeding practices and the risk of asthma at age 5 years.	the benefits of breastfeeding and on introduction of solids after 4-6 months. Data were collected on breastfeeding and introduction of solids during home visits. Information on allergic outcomes at 5 years of age was	months and asthma.
Zutavern et al. [104] (2008) Germany	Longitudinal (LISA)	Children (n=2073)	To examine whether a delayed introduction of solids (past 4 or 6 months) is protective against the development of asthma at the age of 6 years.	Data was collected for respiratory symptoms, feeding practices, lifestyle and environmental factors.	The results showed no association between delayed introduction of solids and risk asthma.
Kremmyda et al. [105] (2011) United Kingdom	Systematic Review	14 studies	To determine the impact of fish oil consumption on development of asthma and atopy	Systematic review of studies looking at fish oil consumption and asthma.	8 of 14 studies identified reported reduced asthma outcomes associated with fish exposure in the diet. Protective effect varied between 25% and 95%.
Kiefte-de Jong et al. [106] (2012)	Longitudinal	7,210 children, from birth to 48months	To assess whether timing of introduction of fish in the first year of life and	Timing of introduction of fish into the infant's diet was assessed at 12 and 14	Introduction of fish between 6 and 12 months was associated with decreased risk of wheezing at 48 months (OR 0.64 [CI 0.43 – 0.94]) compared to not

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Netherlands			fish consumption afterward were associated with the development of asthma-like symptoms at preschool	months. The presence of asthma-like symptoms were later assessed at the child's age of 36 and 48 months	introducing fish in the first year of life. No introduction of fish in the first year was associated with increased risk of wheeze at 48 months (OR 1.57 CI 1.07 – 2.31), as was introducing fish between 0 and 6 months (OR 1.53 CI 1.07–2.19) compared to introducing fish between 6 and 12 months. There was no association between amount of fish consumed at age 14 months and development of wheeze.
D'Vaz et al. [107] (2012) Australia	Randomised control trial	Healthy term infants of 420 allergic women – from birth to 6months	To investigate the effects of fish oil from birth until 6months of age on allergic outcomes in children at high allergic risk	Infants at high atopic risk received either a daily supplement of fish oil, or a placebo (olive oil), from birth up to the age of 6months. PUFA levels were measured in infants' erythrocytes and plasma, and their mothers' breast milk. Asthma was assessed at 12months of age.	Postnatal fish oil improved infant n-3 (omega-3 polyunsaturated fatty acids) status, but lead to no statistically significant reduction in childhood allergic disease.
Osborn et al. [108] (2012) Australia	Systematic review with meta-analysis	2 eligible studies (total of 226 infants)	To review the evidence for prebiotic supplementation in infants to prevent development of asthma		Meta analysis found no significant difference in infant asthma with the use of prebiotics although significant heterogeneity was found between studies

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Kukkonen et al. [109] (2011) Finland	RCT	1,018 children	To study the effect of probiotic treatment during the first six months of life, on airway inflammation at the age of 5years	1,018 children were given a probiotic combination plus prebiotics, or a placebo, from birth to the age of 6months. Exhaled nitric oxide (FE_{NO}) was measured in 160 children as a surrogate marker of asthma and atopy.	No significant difference in FE_{NO} was found between the probiotic treated and non-treated groups.
Milner et al. [110] (2004) USA	Longitudinal	Children (n=8285)	To determine whether early vitamin supplementation during infancy affects the risk of asthma during early childhood.	Data were collected for breastfeeding, vitamin supplementation, respiratory symptoms and food allergies.	History of vitamin use within first six months of life was associated with an increased risk of asthma in black infants (OR 1.27, 95% CI 1.04-1.56).
Child Diet					
Giovannini et al. [111] (2007) Italy	RCT	Children (n=187; Intervention n=92, control n=95)) aged 2-5 years.	To investigate whether the long term daily consumption of fermented milk containing a specific *Lactobacillus casei* may reduce the occurrence and duration of asthma	Intervention group received fermented milk whereas the control group received non fermented milk. Consumption of other products containing probiotic bacteria was forbidden. Data were	No difference was observed for asthma episodes between the groups.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			modify the immunologic profile of pre-school children with allergic asthma.	collected for respiratory symptoms, abdominal symptoms, any other illness and use of antibiotics. Faecal samples were obtained from a subsample to test for the presence of Lactobacillus casei and immunologic blood assessment was carried out among the study subjects.	
Wijga et al. [112] (2003) Netherlands	Longitudinal	Children (n=2978)	To investigate the role of diet in the development of asthma in pre-school children.	Food frequency data gathered at two years of age. Data was collected for asthma symptoms at age 3 years.	Prevalence of wheezing and asthma at 3 years of age was lower in children who consumed full cream milk daily (3.4%) compared to those who did not (5.6%) OR=0.59, 95% CI 0.40-0.88.
Kummeling et al. [113] (2008) Netherlands	Longitudinal	Children (n=2384) followed from birth to 2 years of age.	To investigate whether early life organic food consumption was associated with the development of atopic manifestations in the first two years of life.	Data collected on organic food consumption in second year of life, history of eczema and wheeze and serum total IgE antibodies.	Wheeze not associated with consumption of an organic diet.
Patel et al. [114]	Longitudinal	Children (n=861)	To investigate whether	Questionnaire data were	There was no association between antioxidant intakes

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
(2009) UK	(MAAS)	followed from birth to 8 years of age.	dietary antioxidant intake at age 5 was related to atopy at age 5 and 8 years of age.	gathered for respiratory symptoms and dietary intake. Skin prick tests were carried out to test for allergens.	and wheeze.
Tromp et al. [115] (2011) Netherlands	Longitudinal	6,905 preschool children- followed from birth to the age of 4years	To examine whether different childhood dietary patterns are associated with respiratory symptoms in Dutch children up to 4 yrs of age.	At the child's age of 14 months (±2 months) parents were asked to complete a food frequency questionnaire. Dietary patterns were then classified as Western (associated with refined grains, soups and sauces, savoury and snacks, other fats, sugar-containing beverages and meat) or health conscious (associated with starchy foods, fruit, vegetables, potatoes, vegetable oils, fish, legumes and meat).Data on asthma-related symptoms were obtained by questions adapted from the "International Study of	High adherence to the “Western” dietary pattern was significantly associated with frequent shortness of breath (RR 1.43 CI 1.01 – 2.03) at age 2 yrs. High adherence to the “Western” dietary pattern was also significantly associated with frequent wheeze (RR 1.39 CI 1.02 – 1.89) and frequent shortness of breath (RR 1.66 CI 1.24 – 2.21) at age 3 yrs. However, the association between the “Western” dietary pattern and frequent shortness of breath at the age of 2 and 3 yrs was mainly explained by confounding variables. High adherence to the “Western” dietary pattern was also significantly associated with frequent wheeze (RR 1.70 CI 1.22 – 2.36) and shortness of breath (RR 1.44 CI 1.03 – 2.01) at age 4 yrs. However, this association was again mainly explained by confounding variables. After adjustment for total energy intake, high adherence to the “Western” dietary pattern remained significantly associated with frequent wheeze (RR 1.47 CI 1.04 – 2.07) at 3 yrs of age.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
				Asthma and Allergies in Childhood" (ISAAC) core questionnaires on asthma at the age of 2, 3 and 4 yrs.	
Willers et al. [116] (2010) Netherlands	Longitudinal	2,870 children from birth to the age of 8 years	To investigate whether asthma or atopy outcomes at 8 years of age were associated with long-term dietary exposure, and whether associations were different for consumption at early or later age	Dietary intake was collected using annual questionnaires from the age of 2 to 8years. The intakes of interest were fruit, vegetables, brown/wholemeal bread, fish, milk, butter and margarine. Early age was defined as 2-3years, and late age was defined as 7-8years. Associations between early age and late age, and long-term intake, asthma and atopy at 8years of age were calculated.	Their results showed that fruit consumption at early age was associated with reduced asthma symptoms (OR per 1 consumption day per week increase 0.93, CI 0.85–1.00). Long-term fruit intake is inversely associated with asthma symptoms (OR 0.90 CI 0.82 – 0.99). There were no consistent associations between diet and outcomes for other foods
van Oeffelen et al. [117] (2011) Netherlands	Longitudinal	Children from birth until 8years of age-n=372 in the 4year-old group, and	To investigate the cross-sectional and prospective associations between serum concentrations of	From a 'Prevention and Incidence of Asthma and Mite Allergy birth cohort', serum nutrient	There was a trend towards decreased asthma incidence in children with higher serum magnesium levels, but this did not reach statistical significance. At age 4, higher serum vitamin D levels were associated

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
		n=328 in the 8year-old group	magnesium, vitamin D, selenium and zinc, and prevalence of asthma atopy.	concentrations of magnesium and vitamin D were available for a 4yr-old subgroup and for an 8yr-old subgroup. Questionnaires about the child's asthma symptoms and corticosteroids use were answered annually, until the age of 8years.	with decreased risk of asthma at 8 years (OR for tertile 1 vs tertile 3 0.45 [0.32, 0.57]), however at age 8, higher serum vitamin D levels were associated with increased risk of asthma (OR for tertile 1 vs tertile 3 2.14 CI 0.67 – 6.82)
Infections					
Illi et al. [118] (2001) Germany	Longitudinal (MAS)	Children (n=1314) followed from birth to 7 years of age	To investigate the association between early childhood infections and the subsequent development of asthma.	Data on asthma and asthmatic symptoms were gathered from questionnaires. Information was also sought on infectious diseases in the first years of life. Blood samples were tested annually for specific IgE and bronchial histamine challenge was performed at 7 years of age.	Repeated lower respiratory tract infections showed a positive association with wheeze up to 7 years of age (OR 3.37, 95% CI 1.92-5.92). Children with two or more episodes of rhinitis before the age of one were less likely to have doctor's diagnosis of asthma (OR 0.52, 95% CI 0.29-0.92).

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Jackson et al. [119] (2008) USA	Longitudinal	Children (n=259) followed from birth to 6 years of age.	To define the relationship between specific viral illnesses and early childhood asthma development.	Nasopharyngeal mucus samples were collected at clinic visits and during acute respiratory illnesses. Nasal specimens were analyzed for respiratory viruses. Allergen specific IgE was measured for dust mite and skin prick testing was performed to test for aeroallergens.	From birth to 3 years of age wheezing with RSV was associated with an increased risk of asthma at 6 years of age (OR 2.6 [1.0, 6.3], wheezing with rhinovirus (RV) (OR 9.8 [CI 4.3, 22.0]) and wheezing with both RSV and RV (OR 10.0 [4.5, 22.2]).
Kusel et al. [120] (2007) Australia	Longitudinal	Children (n=198) followed from birth to 5 years of age	To examine the relationships between early life respiratory viral infections, atopic sensitization and development of asthma.	Data gathered on episodes of infections, samples were collected for postnasal aspirates for viral identification.	Any wheezy or febrile lower respiratory tract infection with rhinovirus was associated with a significantly increased risk of doctor-diagnosed asthma at 5 years (OR 2.9, [1.2-7.1], p=0.02).
Stensballe et al. [121] (2009) Denmark	Longitudinal	Children (twins n=8280 pairs) followed from birth to 5 years of age.	To examine the causal direction of association between RSV hospitalization and asthma.	Information from RSV hospitalization and asthma status gathered from twin registry.	Risk of asthma increased 6 to 8 fold in the 2 months following hospitalization for RSV but this risk disappeared 1 year after initial hospitalisation.
Caudri et al. [122]	Longitudinal	Children (n=3963) followed up to 8	To study the effects of day-care on development	Data gathered for sociodemographic factors,	Early day care as a proxy for respiratory infections increased the risk of wheeze up to 4 years of age but

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
(2009) Netherlands		years of age	of asthma and allergic sensitization during first 8 years of life.	health indicators and day care use.	fewer symptoms between the ages of 4-8 years. No protection was observed for asthma symptoms at 8 years of age (OR 0.99, 95% CI 0.74-1.32).
Midodzi et al. [123] (2010) Canada	Longitudinal	8499 children aged <2 years followed up to 5 years of age	To relate early life exposures to asthma outcome at five years	Questionnaire based study	Early day care attendance associated with reduced asthma risk (HR 0.85, 95% CI 0.74-0.98)
Hesselmar et al. [124] (2013) Sweden	Longitudinal study	184 children followed from birth to 36 months	To examine whether the mode by which the parents clean their infant's pacifier affects the risk of allergy development in the infant.	Data were gathered for feeding practices, weaning foods, use of and cleaning practices for the pacifiers, blood samples for allergen specific antibodies and information on diagnosis of wheeze and asthma.	Children whose parents cleaned their pacifiers by sucking it were less likely to have wheeze (OR 0.12, 95% CI 0.01-0.99) at 18 months.
Alcantara-Neves et al. [125] (2012) Brazil	Longitudinal study	1128 children 4-11 year old	To investigate the effect of single or multiple infections on atopy and wheeze in urban children from Latin America.	Data were gathered for specific IgE and skin prick tests, wheezing, infections by 8 pathogens using serology and stool examination.	Isolated infections or pathogen burden were not associated with the prevalence of atopic or non atopic wheeze.
Medications					

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Antibiotics					
Murk et al. [126] (2011) USA	Systematic review	20 studies	To evaluate the evidence of association between antibiotic exposure during pregnancy or in the first year of life and risk of childhood asthma.		Results from the review supported the increased risk associated with use of antibiotics during pregnancy (odds ratio 1.24 [1.02, 1.50]) or infancy (odds ratio 1.52 [1.30, 1.77]) but authors acknowledge the role played by reverse causality and protopathic bias.
Penders et al. [127] (2011) Netherlands	Systematic review	21 longitudinal studies	To review longitudinal studies and describe how outcome definition, reverse causation and confounding by indication affect the association between antibiotic use in early life and development of wheeze or asthma		Overall OR 1.27 [95% CI 1.12, 1.43] and reduced to 1.12 [0.98, 1.26] when reverse causation and confounding by indication considered.
Heintze et al. [128] (2013) Germany	Systematic review	64 studies	To review the evidence suggesting an association between early childhood use of antibiotics and paracetamol and development of asthma		Studies showing a link between early use of antibiotics and paracetamol and development of asthma are likely to reflect bias.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Paracetamol					
Heintze et al. [128] (2013) Germany	Systematic review	64 studies	To review the evidence suggesting an association between early childhood use of antibiotics and paracetamol and development of asthma		Studies showing a link between early use of antibiotics and paracetamol and development of asthma are likely to reflect bias.
Etminan et al. [129] (2009) Canada	Systematic review	19 studies	To quantify the association between acetaminophen use and the risk of asthma in children and adults.		Increased risk of asthma and wheezing was observed following prenatal acetaminophen use OR 1.28 [1.13, 1.39] and OR 1.50[1.10, 2.05].
Eyers et al. [130] (2011) New Zealand	Systematic review	6 studies	To review the evidence from studies investigating the association between paracetamol use in pregnancy and childhood asthma		Any antenatal use of paracetamol was associated with an increase in risk of childhood asthma (OR 1.21 [1.02-1.44]).
Other maternal medications during pregnancy					
Kallen, B et al[131]	Longitudinal Study	685,015	To investigate the maternal use of drugs during the 2nd and 3rd trimesters with risk for	Childhood asthma was identified from the Swedish National Prescription Register and maternal drug	There was a positive association between risk of childhood asthma and maternal use of drugs for gastroesophageal reflux (adjusted OR 1.32 [1.12,1.55])

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
(2013) Sweden			childhood asthma.	use during the latter part of the pregnancy from antenatal records.	and with opiates (adjusted OR 1.56 [1.05, 2.34]).
In Utero Exposures					
Li et al [132] (2011) USA	Longitudinal	734 pregnant women (offspring followed up until age 13)	To determine a possible link between exposure to electromagnetic fields in utero and development of childhood asthma	Women wore a metre for a 24 hour period during the first or second trimester of pregnancy to measure exposure to electromagnetic fields. Children were followed up until they were diagnosed with asthma or turned 13	A 1 unit increase in in utero electromagnetic exposure was linked with increased in likelihood of developing asthma by age 13 (HR 1.15 [1.04, 1.27]). Children whose mothers had a medium magnetic field level had a 74% increased rate of developing asthma (HR 1.74 CI 0.93 - 3.25) compared with those whose mothers had a low level. Children whose mothers had a high magnetic field level during pregnancy had more than a 3.5-fold increased rate of developing asthma (HR 3.52 CI 1.68 - 7.35)
Stolevik, SB et al[133] (2013) Norway	Longitudinal Study	114 children followed for 3 years	To determine whether prenatal exposure to polychlorinated biphenyls and dioxins from the maternal diet are associated with the development of immune-related diseases in childhood	Data was collected using an annual questionnaire and maternal intake of the toxicants was calculated using a food frequency questionnaire	Maternal exposure to dioxin-like PCBs and dioxin was found to be associated with an increased risk of wheeze at (OR 2.71 CI 1.21–6.04) at age 0-3. Maternal exposure to non dioxin-like PCBs was associated with increased risk of and wheeze (OR 3.20 CI 1.42–7.22) at age 0-3.

Donohue, KM et al[26] (2011) USA	Longitudinal Study	568 pregnant women followed up until children were 12 years of age	To determine whether BPA exposure is associated with increased risk of physician diagnosed asthma	Maternal spot urine samples were collected during the third trimester of pregnancy and from children at ages 3, 5 and 7. BPA urinary concentrations were measured.	Urinary BPA concentrations at ages 3, 5 and 7 were associated with increased odds of asthma. (OR, 1.5 [95% CI, 1.1-2.0], P = .005; OR, 1.4 [95% CI, 1.0-1.9], P = .03; and OR, 1.5 [95% CI, 1.0-2.1], P = .04 respectively. Prenatal urinary BPA concentrations were inversely associated with wheeze at 5 years.
Gascon et al[134] (2012) Spain	Longitudinal	1455 mother-child pairs	To examine whether in utero exposure to dichlorodiphenyldichloroethylene (DDE) increases infant wheeze	Maternal serum levels of DDE, organic compounds and PCBs were measured during pregnancy. Mothers completed a questionnaire on their child's health at 12-14 months of age.	Wheeze (defined as any reported wheeze over the past 6 months) increased with every 10% increase in DDE concentration (RR 1.11 [1.00, 1.22]).
Spanier, AJ et al [135] (2012) US	Longitudinal Study	396 mother-infant pairs	To examine the relationship between prenatal BPA exposure and wheeze in early childhood	BPA concentrations in serial maternal urine samples were measured and parent-reported child wheeze was assessed every 6 months for 3 years. Generalized estimating equations with a logit link were used to evaluate the association	Mean prenatal BPA above the median was positively associated with wheeze at 6 months ((AOR) = 2.3; 95% confidence interval (CI): 1.3, 4.1) but not at 3 years (AOR = 0.6; 95% CI: 0.3, 1.1)

Table 2. Quality assessment score. Global rating 1=Weak; 2=Moderate and 3=Good

Study Ref.	Selection Bias	Study Design	Confounders	Blinding	Data Collection Methods	Withdrawals and Drop-outs	Global Rating
Jedrychowski [3]	1	1	2	3	1	1	2
Haberg[7]	2	2	2	1	2	2	2
Stolevik [25]	3	2	1	3	3	1	3
Tischer[36]	1	1	1	2	1	1	1
Bolte[58]	3	2	2	1	1	2	2
Phipatanakul[59]	3	2	2	2	1	1	2
Harley[65]	3	2	2	2	3	1	3
Patel[75]	2	2	2	3	3	2	3
Camargo[87]	3	2	2	2	1	1	2
Silvers[94]	2	2	2	2	1	1	2
Virtanen[102]	2	2	2	2	3	2	2
Wiiga[118]	1	2	2	3	1	2	2
Caudri[122]	3	2	2	2	1	3	3
Heintz[129]	1	1	2	2	2	2	1

Search strategy

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2. wheeze.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
3. atopy.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
4. hayfever.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
5. Allergens/
6. Bronchial Spasm/
7. reactive airway disease.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
8. Bronchial Hyperreactivity/
9. environmental factors.mp.
10. environmental influences.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
11. environmental exposure.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
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14. 10 and 12
15. 11 and 12
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18. 1 or 2 or 3 or 4 or 6 or 7 or 8
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20. in utero exposure.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
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24. parental smoking.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
25. 18 and 24
26. Cotinine/
27. 18 and 26
28. 18 and 21
29. 19 or 23 or 25 or 27 or 28
30. limit 29 to (english language and humans and ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)") and english and humans)
31. from 30 keep 1-599
32. Nitrogen Dioxide/
33. gas fire*.mp.
34. cooker*.mp.
35. hob*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
36. 32 or 33 or 34 or 35
37. 18 and 36
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43. dry cleaning.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
44. Chlorine/
45. swimming pool*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

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47. Benzene/
48. resin*.mp.
49. varnish.mp.
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70. 18 and 52

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193. 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192
194. 18 and 193

195. exercise.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
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207. corona virus.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
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209. 202 or 204 or 206
210. diet.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
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212. sulphite*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
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227. 225 or 226
228. 18 and 227
229. drug*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
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234. NSAID*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
235. 231 or 232 or 233 or 234
236. 18 and 235
237. obesity.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
238. 18 and 237
239. 29 or 131 or 136 or 149 or 166 or 194 or 196 or 198 or 200 or 209 or 224 or 228 or 236 or 238
240. 9 or 10 or 11
241. 18 and 240
242. 239 or 241
243. 74 or 242

244. limit 243 to (("all infant (birth to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)") and english and humans and (case reports or classical article or comparative study or congresses or consensus development conference or consensus development conference, nih or controlled clinical trial or "corrected and republished article" or government publications or guideline or historical article or introductory journal article or journal article or meta analysis or multicenter study or patient education handout or periodical index or randomized controlled trial or research support, nih, extramural or research support, nih, intramural or research support, non us gov't or research support, us gov't, non phs or research support, us gov't, phs or "review" or "scientific integrity review" or twin study or validation studies))

245. from 244 keep 6033,6045,6055,6062,6065,6091,6122,6150,6166,6172,6179,6225,6229-6230,6245,6249,6304,6307-6309,6315,6317,6346,6413-6414,6428,6435,6441,6453,6516,6551-6552,6574,6581,6585,6588,6599,6622,6641,6660,6699

246. from 244 keep 6710,6783

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not present
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	On line supplement
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	On line supplement
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Multiple outcomes described

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not appropriate

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	On line supplement
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Throughout results
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Pages 6-7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	On line supplement
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	On line supplement
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Pages 6-19, no forest plot as meta analysis not possible
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	See above
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	On line supplement
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Throughout results
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 19

PRISMA 2009 Checklist

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Pages 19-21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Pages 19-21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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A Systematic Review of Associations between Environmental Exposures and Development of Asthma in Children Aged up to Nine Years

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Word count: 5745

ABSTRACT

Objectives. Childhood asthma is a complex condition where many environmental factors are implicated in causation. The aim of this study was to complete a systematic review of the literature describing associations between environmental exposures and the development of asthma in young children.

Setting. A systematic review of the literature up to November 2013 was conducted using key words agreed by the research team. Abstracts were screened and potentially eligible papers reviewed. Papers describing associations between exposures and exacerbation of pre-existing asthma were not included. Papers were placed into the following predefined categories: second hand smoke(SHS), inhaled chemicals, damp housing/mould, inhaled allergens, air pollution, domestic combustion, dietary exposures, respiratory virus infection and medications.

Participants. Children aged up to nine years.

Primary outcomes. Diagnosed asthma and wheeze.

Results. 14,691 abstracts were identified, 207 papers reviewed and 135 included in the present review of which 15 were systematic reviews, 6 meta analyses and 14 were intervention studies. There was consistent evidence linking exposures to SHS, inhaled chemicals, mould, ambient air pollutants, some deficiencies in maternal diet and respiratory viruses to an increased risk for asthma (odds ratio typically increased by 1.5-2.0). There was less consistent evidence linking exposures to pets, breast feeding and infant dietary exposures to asthma risk and although there were consistent associations between exposures to antibiotics and paracetamol in early life, these associations might reflect reverse causation. There was good evidence that exposures to house dust mite (in isolation) was not associated with asthma risk. Evidence from observational and intervention studies suggest that interactions between exposures were important to asthma causation, where the effect size was typically 1.5-3.0.

Conclusions. There are many publications reporting associations between environmental exposures and modest changes in risk for asthma in young children and this review highlights the complex interactions between exposures which further increases risk.

Strengths and limitations of this study

- This is the first systematic review of the whole literature relating early life environmental exposures to childhood asthma causation
- A high level of evidence was available (i.e. systematic reviews, meta analyses and/or intervention studies) for many exposures classes
- More than 70% of papers identified described associations observed within single populations
- The observational literature is likely to be affected by publication bias, reverse causation and confounders.
- Studies describing outcomes in children where the mean age was >9 years were not included

INTRODUCTION

Asthma is a common chronic condition in children where environmental and genetic factors are implicated in causation. The rapid rise in asthma during the 1980s and 1990s [1] was too abrupt to be explained solely by change in prevalence of genetic variations. Changing environmental exposures appear to be relevant to the high prevalence of asthma in the Western world [2], although some exposures are likely to be effective via epigenetic mechanisms [3]

Many environmental exposures have been linked to asthma causation, including allergens [4], smoking [5], dietary factors [6] and respiratory infections [7]. More recently, evidence has emerged to suggest that asthma causation may involve interactions between different environmental exposures [8,9] and/or environmental exposures and atopy [10]. Due to the many challenges of relating even a single exposure to asthma causation, there is very little synthesis in the literature of multiple environmental exposures and asthma causation.

The Environmental Determinants of Public Health in Scotland (EDPHiS) was commissioned in 2009 to quantify the evidence on the connections between the environment and key aspects of health of children in order to inform the development of public policy. Asthma was identified as a priority along with obesity, unintentional injury and mental health. The overall aim of this systematic review was to capture all of the literature associating early environmental exposures and asthma development in children up to nine years of age; this cut off was chosen to avoid the effects of puberty and active smoking on asthma causation. A recent paper describes associations between environmental exposures and asthma control and exacerbation[11]. Our specific aims were (i) to describe the magnitude of association between the development of asthma and environmental exposures (ii) to explore evidence of interactions between environmental exposures.

METHODS

Study design

A workshop attended by senior researchers from government and academia, health practitioners and policy professionals identified environmental influences considered important to on causation and exacerbation of asthma (previously described[11], Table I). By extrapolation from approaches to assessment of causation in workplace exposures for compensation purposes (http://iiac.independent.gov.uk/about/index.shtm), we considered an exposure which increased the risk for asthma by at least two-fold as having at least a modest effect size.

Search strategy and data sources

The search strategy for Medline is provided in the supplement and has also been described previously[11]. Two reviewers (SD and ED) searched the electronic databases (including Medline, Embase, Cochrane controlled trials register (CCTR) and CINHAL) and reference lists of other studies and reviews between January 2010 and April 2010. Updated searches were carried out in July 2011 and November 2013. No date limits were applied to the search strategy. Studies identified from searching electronic databases were combined, duplicates removed and papers were screened for relevance to the review based on the information contained in the title and abstract. Abstracts were screened by a second reviewer (ST) and potentially eligible papers were identified.

Inclusion/ exclusion criteria

Studies were included if a) they captured exposure to an environmental factor identified as potentially relevant to the development of asthma b) the mean age of asthma outcome was <9 years, outcomes include diagnosis of asthma or data related to health care utilization (hospital admissions, drug use) and morbidity and functional status, lung function tests, measures of self-perception of health status (symptom free days) and wellbeing and quality of life; c) the study design was either a meta analysis, systematic review, randomized control trials, non randomized control

trials and cohort studies. If no evidence was apparent for an exposure, then studies meeting the lower Scottish Intercollegiate Guidelines Network criteria were considered, i.e. case control and case report studies (http://www.sign.ac.uk/guidelines/fulltext/50/annexb.html 21st June 2014). Clinical trials were excluded.

Study selection and data extraction

The full text of references identified as potentially relevant were obtained and papers included by applying the inclusion criteria, sometimes after discussion between reviewers (SD and ST). Papers which were included in a systematic review were not included. For cohort studies where outcomes were reported at increasing ages after one exposure, only the most recent paper was included. A summary table included the following details from studies: study design, characteristics of the study population, the study objectives, the key outcome(s) reported including what the primary asthma outcome, eg wheeze, physician diagnosed asthma.

Quality assessment

Quality assessment of included papers was carried out using "Effective public health practice project quality assessment tool for quantitative studies" (http://www.ephpp.ca/PDF/Quality%20Assessment%20Tool_2010_2.pdf Accessed June 2014**).** Results are presented in the supplement, due to the relatively large number of studies identified a random 10% were chosen for quality assessment.

RESULTS

Literature search

There were 14691 references identified from electronic databases and other studies. There were 207 full papers reviewed and 135 studies met the inclusion criteria (Figure 1). There were 15 systematic reviews, 6 meta analyses, 91 cohort studies, 14 intervention studies included, 5 case-

control studies and 3 cross sectional studies. There no case series was included. There were 61 studies from Europe (including 3 meta analyses), 32 from North America, 13 studies from Australia or New Zealand, 3 from Japan and single remaining papers from UAE, India, Qatar, South Korea, Mexico, Taiwan and Brazil. There were 84 (63%) studies published in the last five years, i.e. from 2009. Table 1 in the supplementary file presents details of the included studies, including number and mean age of children included, the respiratory outcome reported and the effect size. No studies were identified for industrial combustion, fireworks, bonfires, vacuuming, air conditioning or air humidifiers. Table 2 presents the effect size of the exposures on asthma risk from the studies identified. Table 3 presents results from studies where interactions between exposures were associated with altered asthma risk

Second Hand Smoke

Antenatal exposure

One meta analysis and five cohort studies were identified and most found exposure was associated with increased risk for asthma. The meta analysis[12] identified 735 exposed children and concluded that exposure was associated with an increased risk for asthma at six years (OR 1.7). The cohort studies found risk was increased by 1.13[13] and 2.1[14] at 2 years and 1.4 at seven years[15]. One study of infants born 3-4 weeks prematurely found increased risk for wheeze at three years only among those exposed to SHS (odds ratio 4.0, table 3) [16]. One study found no association between antenatal exposure and risk for symptoms[17].

Post natal exposure

One systematic review and six cohort studies were identified and all reported that exposure was associated with increased asthma risk. The systematic review concluded that exposure to tobacco smoke was associated with an increased risk of 1.3 among children aged 6-18 years[5]. Postnatal exposure was associated with increased risk for wheeze between 1.2 [18] and 2.9 [17] and asthma at five

years 1.7 (table 3)[19]. The study from Japan[17] found a link between postnatal but not antenatal maternal smoking and wheeze at 16-24 months. One study [18] found that postnatal paternal smoking was a risk factor for wheeze (RR 1.14 [1.04-1.24]) independent of maternal smoking. Another study reported an interaction between short duration of maternal education and SHS exposure[19]. A final study found that increasing exposure to fine particulates ($PM_{2.5}$) and urinary cotinine, products of tobacco combustion, were positively linked to risk for infant wheeze[20].

Domestic combustion

Two cohort, one cross sectional and two case-control studies were identified and there was inconsistent evidence between exposure and asthma risk. One cohort study retrospectively modelled exposure to gas cooking at five years to asthma in four year olds and found no association[21]. In a second cohort study, increasing exposure to domestic $PM_{2.5}$ was associated with increased risk for new onset wheeze over the next three years (OR 1.5 per quartile increase in exposure), adjusting for SHS exposure[22]. A cross sectional study found an association between detectable indoor air sulphur dioxide (SO_2) and risk for wheeze (OR 1.8) at age six-ten years[23]. This study found no link between burning incense and asthma symptoms[23] and this was consistent with a case-control study which found no evidence for exposure to Bakhour incense and risk for asthma [24]. A case-control study from India[25] found evidence for increased asthma among children (OR 4.3) living in homes where biomass was used for cooking compared to other homes.

Inhaled Chemicals

One meta analysis, one cohort study, one cross sectional study and two reports from one case-control study were identified and all found evidence of exposure being associated with increased asthma risk. The meta analysis of data from seven studies concluded that increasing formaldehyde exposure was associated with increased asthma risk (OR 1.2 per 10µg/m^3 increase)[26]. A cohort study[27] used redecoration of the apartment as a proxy for exposure to volatile organic compounds

(VOCs) and found an increase in risk for obstructive bronchitis (OR 4.2). Simultaneous exposure to ETS and cats added to the risk (OR 9.1, table 3)[27]. One cross sectional study [28] found an association between indoor exposure VOC of microbial origin (MVOC's) and plasticizers and risk of asthma (mean increased risk for asthma 2.1 per microg/m^3 of total MVOC). Two scientific papers on the same study[29,30] found domestic exposure to formaldehyde, benzene and its compounds and toluene was positively associated with asthma risk (3% increase per 10 microg/m^3 increase in formaldehyde exposure).

Chlorinated swimming pools

Three cohort studies were identified and results were apparently conflicting. Exposure to chlorinated swimming pools in infancy and childhood was associated with reduced risk for current asthma at seven years (OR 0.5)[31]. A second study found no link between exposure to chlorine through swimming and asthma at six years of age[32]; those who did not attend swimming during the first year of life were more likely to have asthma.

Other chemicals

In this broad category there was one systematic review, two cohort studies, two cross sectional studies and a case-control study; all found evidence of exposures being linked to increased asthma symptoms. A systematic review of seven studies of children aged up to 12 years found a positive association between polyvinyl chloride exposure in dust samples and asthma (OR 1.6) [33]. One study (using the same cohort mentioned above[31]) created a composite household chemicals exposure score (including chlorine/chloride exposure), and found a positive association between exposure and risk of incident wheeze after 2.5 years of age (OR 1.7)[34]. Two cohort studies related antenatal and current exposures to asthma risk: high exposure to pyrene was associated with increased asthma risk in 5-6 year olds (OR 1.9)[35], and this association was only apparent in non-atopic children and maternal exposure during pregnancy was not related to asthma (table 3); maternal Bisphenol A exposure during pregnancy was inversely associated with wheeze at five years (OR 0.7) but not at seven years, however the child's current exposure was positively association with this outcome (OR

1.4)[36]. Living close to a petrochemical plant was associated with an increased risk for asthma (OR 2.8) [37]. A case-control study found increased wheeze in 6-14 year olds living close to an oil refinery compared to controls (OR 1.7)[38].

Damp housing/mould

One systematic review, one meta analysis plus four cohort studies were identified and early exposure was consistently associated with increased risk for later asthma symptoms. The systematic review included data from 16 studies and concluded that exposure to visible mould was associated with increased risk for asthma (OR 1.5) [39]. The meta analysis of 8 European birth cohorts found an association between exposure to visible mould or dampness and increased wheeze at two years (OR 1.4) but not significantly at 6-8 years (OR 1.1)[40]. The cohort studies found mould exposure in early life to be associated with increased risk for asthma at three years (OR 7.1) [41] and seven years (RR 2.4 for presence of any mould[42] and OR of 2.6[43] and 1.8 [44] per unit increase in mouldiness index).

Inhaled allergens

Indoor exposures

Multiple exposures

There were five intervention studies and eight additional cohort studies identified. One intervention randomised newborns to house dust mite (HDM) reduction measures, avoidance of cows milk or both or neither and found no difference in asthma incidence at age five years across the four groups[45]. A second study also modified post natal exposure to cows milk protein (and other dietary allergens) and HDM and the intervention group had trends for reduced wheeze (OR 0.4 [0.2, 1.08]) at eight years[46]. A third intervention study reduced exposures to SHS, inhaled and ingested allergens and promoted breastfeeding but found no difference in asthma outcome age six years[47]. The fourth intervention modified exposures to antenatal and postnatal oily fish, SHS and dampness and observed reduced asthma risk at two years for the intervention group (OR 0.7)[48]. The fifth study

modified antenatal and postnatal exposures to HDM, pets, SHS, promoted breast feeding and delayed weaning and asthma risk at seven years was reduced in the intervention group (OR 0.4)[49]. Five observational studies related early life HDM exposure plus other "dust" exposures to asthma: increased HDM and LPS exposures were independently associated with increased symptoms by seven years; HDM ≥10 microg/g associated with increased risk for asthma (OR 3.0) and each quartile increase in LPS associated with increased risk for lifetime wheeze(OR 1.2) [50] and exposure to higher concentrations of cat allergen (but not to HDM) and asthma by six years of age OR for third versus lowest exposure quartile 2.6 [1.3, 5.4] [51]; other studies found no association between (i) infantile exposure to HDM and cat and cockroach allergen and wheeze at two years[52] (ii) HDM, cat and dog allergen exposure and wheeze at four years[53] and (iii) HDM and cat exposure and asthma at seven years [54]. One study reported increasing cockroach allergen exposure in infancy was positively associated with wheeze by age five years (OR 1.8) and, independently, the presence of a dog and higher concentrations of cat allergen exposure were associated with reduced wheeze risk (OR 0.3 and 0.6)[55]. Dog allergen exposure in infancy was not associated with asthma at seven years *per se* but was associated with asthma in combination with exposure to SHS (OR 2.7) or elevated NO_2 (OR 4.8) [56]. A final study observed interactions between exposures to SHS, breast feeding and recurrent respiratory infections and asthma[57].

Pet exposure

There were two systematic reviews, one meta analysis and six cohort studies identified and the results were highly inconsistent. One systematic review of nine studies concluded that exposure to pets around the time of birth may reduce risk for allergic disease (including asthma) where there is no family history of asthma, but no effect size was given[58]. The second systematic review concluded that exposure to cats reduced the risk for asthma (OR 0.7) and to dogs increased asthma risk (OR 1.1)[59]. The meta analysis found no evidence for cat exposure in early life being linked to asthma risk at age 6-10 years, there was a non-significant trend for dog ownership to be associate with reduced asthma risk (OR 0.8 [0.6, 1.0]) [60]. The cohort studies found early cat exposure to be associated with

increased severe asthma at four year (OR 4.7)[61], and reduced wheeze by age five years (OR 0.6[62] and 0.3[63]), increased wheeze at seven years (OR 1.2) [64] and not association with asthma risk at four[65] or eight years[66] ; in a post hoc analysis early exposure to dog was linked to reduced late onset wheeze at 4 (OR 0.4 [0.2, 1.0])[65]. There was apparent synergy between exposure to both high concentrations of cat allergen and increased risk for severe asthma at 4 years (OR 10.8 [2.0, 59.6]) [61].

Other exposures

There was one systematic review relating exposure to living on a farm to asthma risk, data from 39 studies were identified and despite differences in definitions for asthma and associations with exposure to living on a farm, there was a 25% reduction in risk for asthma for children living on a farm compared to controls (no confidence intervals presented)[67]. A cohort study found an association between lipopolysaccharide (LPS) concentration in mother's mattress when the infant was three months old was associated with repeated wheeze by two years of age (OR 1.5 comparing highest with lowest quartile for exposure)[68]. A second cohort study reported an association between increased current exposure to mouse allergen and wheeze at seven years of age (OR 1.4)[69] ; there was no association between mouse allergen exposure in infancy and later wheeze. A third small cohort reported no association between exposure to cockroach allergen in infancy and wheeze in the first two years of life [52]. Observational studies report associations between exposure to feather quilt in infancy and reduced asthma at four years compared to non-feather quilt (OR 0.4)[70] and that a greater number of synthetic items of bedding (known to be HDM rich) during infancy was associated with increased risk for a history of asthma by 7 years (OR 1.8)[71].

House dust mite exposure

There were two intervention studies[72,73] and one observational study[74] and none found an association between exposure in infancy[72,73] or by two years of age[74] and asthma at 3[73], 6-7[74] or eight years of age[72].

Outdoor allergens

Three cohort studies were identified and all found exposure was related to increased asthma risk. One study related fungal spores and pollen concentrations at the time of birth to wheeze at age two years over 12 months in certain months of the year and those born in autumn to winter (the fungal spore season) were at increased risk for wheezing (OR 3.1)[75]. A second study reported an association between increased grass pollen exposure between 4 and 6 months of age and increased asthma at seven years of age (OR 1.4)[76]. The third study related tree canopy cover (a source of tree pollen and also of altered airflow and air quality) in infancy to asthma at seven years and found a positive association (RR 1.2)[77].

Air pollution

There was one meta analysis and eight additional cohort studies and whilst pollutants associated with combustion were associated with increased asthma risk, no single pollutant was consistently identified. The meta analysis found that exposure to Nitrogen dioxide (NO_2, OR 1.05), Nitric Oxide (OR 1.02), and Carbon Monoxide (CO, OR 1.06) were associated with higher prevalence of diagnosis of childhood asthma. Exposures to SO_2 (OR 1.04) and particulates (OR 1.05) were associated with a higher prevalence of wheeze in children[78]. Ambient lifetime CO exposure, but not NO_2, ozone or particulates with mass less than 2.5 microns ($PM_{2.5}$), was associated with increased risk for wheeze at five years (OR 1.04 per ppm increased CO)[79]. A second cohort study found that ambient exposure to NO_2, but not ozone, SO_2, $PM_{2.5}$ and PM_{10}, was associated with increased asthma risk at three years (OR 1.2 per 5ppb increase) [80]. A third study related averaged life time exposure to ozone, CO, NO_2, SO_2 and PM_{10}) and found no association with asthma in seven year olds for the whole population but among the 10% with previous bronchiolitis asthma risk was increased (OR approximately 7) in association with higher exposures to ozone, CO and NO_2[81], table 3. Exposure to traffic related particles (elemental carbon attributable to traffic) during infancy was associated with increased risk for asthma in three-year-olds (OR 2.0) and co- exposure to high concentrations of

domestic endotoxin increased the risk (OR 3.4) [82]. One study one found increased wheeze prevalence in four year olds among those exposed to stop/go traffic compared to unexposed children (23% versus 11%)[83] and the second found that children with a life time exposure to higher traffic density were more likely to be diagnosed with asthma (OR 1.3)[84]. Exposure to high (> 4.1μg/m^3) levels of $PM_{2.5}$ during infancy were associated with increased risk for asthma in a small cohort (OR 3.1)[85].

Dietary exposures

Maternal diet – food items

There was one systematic review, one intervention study and five cohort studies identified and some food items were linked to childhood asthma risk. The systematic review of 62 studies concluded that there was more convincing evidence for maternal fruit (compared with vegetable) intake during pregnancy to be associated with reduced risk for childhood asthma[86], there was only one study identified relating maternal Mediterranean diet to outcome (persistent wheeze (OR 0.2) at age 6.5 years) and maternal exposure to fish was not included. A small intervention study where pregnant mothers took placebo or fish oil supplement found no difference in respiratory symptoms between treatment groups at one year[87]. A study from Japan found reduced risk for wheeze at 16-24 months for children whose mother's diet had been least "Westernised" (OR 0.6 for comparison with most Westernised)[88]. A Mexican study found a protective effect of fish consumption during pregnancy on atopic wheeze (OR 0.6)[89]. In Denmark, maternal intake of peanuts (OR 0.8) and tree nuts (OR 0.8) was inversely associated with asthma in children at 18 months of age[90]. In Finland, low maternal consumption of leafy vegetables (OR 1.6), malaceous fruits (eg apple, pear, OR 1.5), and chocolate (OR 1.4) were positively associated with the risk of wheeze in five-year-old children[91]. A final study found no association between maternal butter and margarine intake and asthma outcomes in children aged five to six [92].

Maternal diet- specific nutrients

There was one systematic review and 8 cohort studies identified and reduced exposure to some nutrients was associated with increased asthma risk. Meta analysis within the systematic review found that (i) increasing maternal vitamin D intake was associated with reduced risk for wheeze in the last year (OR 0.6, 4 studies) but not asthma at five years (ii) increasing maternal vitamin E intake was associated with reduced wheeze at 2 years (OR 0.7, 3 studies) (iii) increased maternal plasma vitamin A was associated with reduced asthma risk (OR 0.3, 2 studies) and (iv) no evidence for associations between maternal plasma zinc or selenium and asthma outcomes[86]. Of five cohort studies published after the systematic review, four found no evidence linking maternal plasma vitamin D[93-95] or vitamin D intake[96] and asthma; one study found an inverse association between cord plasma vitamin D and risk for wheeze, but not asthma, by age five year (OR 0.95 per 10 nmol/L increase)[97]. One study found maternal fatty acid intake during the third trimester was associated with asthma out come at five years (e.g. higher alpha-linoleic acid and palmitic acid intake associated with ~40% reduced risk) [98]. Other studies found no association between maternal dietary antioxidants[99] or folate[100] and vitamin A[101] supplementation and childhood asthma outcomes.

Exposure to milk during infancy

In addition to the previously described complex interventions where milk exposure was modified, a number of studies were identified where only milk was the exposure of interest and there was evidence that early milk exposure was related to altered asthma risk.

Breast milk. There was one systematic review with meta analysis, two cohort studies and one intervention study identified. Meta analysis of 31 studies found any breast feeding reduced risk for wheeze (OR 0.92) but increased risk for asthma (OR 1.10) [102]. Never breast feeding was associated with increased wheeze by four years (OR 1.4)[103] and exclusive breast feeding was associated with reduced in asthma risk at five (OR 0.9) [104] but not at six years of age. The intervention study found that prolonged breast feeding (up to the age of 12 months) was associated with reduced asthma at

four but not at six years of age[105]. Maternal margarine intake (but not fatty acid or fish intake) whilst breastfeeding was associated with increased risk for asthma at five years (HR 2.0)[98].

Cow's milk formula. There were one systematic review, two intervention studies and one observational study identified. A systematic review of 10 trials concluded that hydrolysed cow's milk formula, but not soya-based milk, reduced risk of wheezing in infancy (RR 0.4]) compared to standard cow's milk formula [106]. Modification of cow's milk formula either by a non-hydrolysing fermentation process or supplementation with fatty acids (arachadonic acid or Docosahexanoic acid) was associated with reduced risk for wheeze by two (13 vs 35%)[107] and three years of age (OR 0.3)[108] compared to standard cow's milk formula. An observational study found no evidence for hydrolysed feed for the first six months reducing asthma risk at three years[109].

Dietary exposures during infancy

There were two systematic reviews, two clinical trials and five observational studies, there were some associations between exposure to some dietary components and altered risk reported. Four observational studies related first dietary exposures to asthma outcomes and one found evidence for early introduction of cereals by 6 months and egg by 11 months was associated with 30-40% risk for asthma at five years[110] and a second study found a direct relationship between age at introduction of oats and risk for asthma at five years (OR 0.4 for earliest versus latest age at introduction)[111]. Two other studies found no association between early or delayed introduction of any solids and asthma risk at 5[112] and 6 years[113]. A systematic review of 14 studies relating fish oil exposure during infancy and asthma (and other allergic outcomes) concluded that exposure was linked to a reduced risk of between 5 and 75%[114]. One cohort study found an association between the introduction of fish between 6 and 12 months and decreased risk for wheezing at 48 months (OR 0.6)[115] however the two previously discussed studies found no association between fish exposure and asthma[112,113] and an intervention study of fish oil supplements in the first six months of life did not change risk for asthma symptoms at 12 months [116]. A systematic review of two trials found no link between infant diet supplementation prebiotics and asthma risk[117], and a trial where infants

were randomised to supplement with probiotic (+/-prebiotic) or placebo also found no difference in asthma risk[118]. One cohort study found no evidence for association between infant vitamin supplements and asthma risk although among African-Americans, supplementation was associated with increased risk (OR 1.3) [119].

Dietary exposure in childhood

There were one RCT and six cohort studies identified and there was limited evidence linking early exposure to later increased asthma risk. Supplementation of milk with fermented milk containing lactobacillus during the first two years did not alter risk for asthma compared to placebo[120]. One observational study found daily exposure to full cream milk at two years reduced risk for asthma one year later (OR 0.6 [0.4, 0.9])[121]. Exposure to organic food during the first two years[122] and dietary oxidant at five[123] and were not associated with altered risk for wheeze at two years or asthma at eight years respectively. Studies from Netherlands found exposure to a "western" diet at 14 months was associated with a increased risk for frequent wheeze at three years (RR 1.5)[124], exposure to fruit in early childhood reduced risk for asthma at eight years (OR 0.93 per item consumed day per week) [125] and that increased plasma vitamin D at four years was associated with reduced asthma risk at eight years (OR for highest vs lowest tertile 3 0.5]) [126] but serum vitamin D levels at eight years were not associated with current asthma risk[126].

Respiratory virus infection

There were six cohort studies identified and there was consistent evidence for infection associated with wheeze or hospitalisation increased asthma risk. Parent reported lower respiratory tract infections during infancy were negatively associated with the risk of asthma at seven years of age in one cohort (OR 0.5) [127]. A cohort study demonstrated that wheeze before four years of age was associated with increased risk for asthma at six years if rhinovirus (OR 9.8) was present[128]; there was a borderline increase in risk if respiratory syncitial virus (RSV) was present (OR 2.6). A second cohort

selected for familial risk for atopy also found rhinovirus positive (but not RSV positive) wheezing lower respiratory tract infection during infancy was associated with increased risk for asthma at age five year (OR 2.9) [129]. A third study observed an increased risk of asthma following infection with RSV, and this risk was higher in the months following the hospitalization and lower with longer duration since hospitalization (e.g. RR 6.2 within two months of hospitalization and 2.2 6-11 months after hospitalization) [130]. Early day care, a proxy for respiratory infections, was not associated with altered risk for asthma at age eight years[131] in one cohort but was associated with reduced asthma risk at four years in a second study (HR 0.9)[132].

Other infections

One small cohort study observed reduced risk for wheeze at 18 months for children whose parents cleaned their dummy/pacifier by sucking it (OR 0.1 [0.01, 1.0]) compared to other cleaning practices [133]. A second cohort study found no evidence for infection in preschool children (either serologically proven or isolated from stool samples) and wheeze by 11 years [134].

Medications

Antibiotics

Three systematic reviews were identified which related antenatal [135] and postnatal [135-137] exposure to antibiotics and asthma outcomes. There was evidence that antenatal and postnatal exposure were associated with increased risk for early asthma symptoms (e.g. OR 1.2 for antenatal exposure and 1.5 for postnatal exposure)[135] but all three SRs concluded that this association was explained by reverse causation. One SR demonstrated that the OR fell from 1.3 to 1.1 when reverse causation was considered[136].

Paracetamol

Four SRs were identified and these linked antenatal [135,138] and postnatal [135-137] exposure to paracetamol to the risk of asthma symptoms. There were associations between paracetamol exposure and the development of asthma OR 1.3[139] and wheeze OR 1.2[138]. The third SR did not present an effect size and suggested that any association was by reverse causation[137].

Other maternal exposures during pregnancy

A whole-population study found treatment during the second and third trimester with the following were associated with increased risk for asthma ; antibiotics (OR 1.1) ; drugs for gastroesophageal reflux (OR 1.3); opiates (OR 1.6); thyroid drugs (OR 1.3); there was no association with paracetamol prescribing[140]. Five cohort studies related various maternal exposures during pregnancy to early childhood wheeze and reported the following associations: exposure to dietary dioxins and polychlorinated biphenyls was associated with increased wheeze by three years (OR 2.7) [141]; exposure to bisphenol A (BPA) was positively associated with a transient increase in wheeze in one study (OR for wheeze at six months 2.3, higher vs lowest exposure) [142] and inversely associate with transient wheeze in a second study (OR for wheeze at five years 0.7 per increase in log transformed BPA)[36] ; each 10% increase in exposure to dichlorodiphenyldichloroethylene (a product of the the pesticide DDT) was associated with increased wheeze at 12-14 months of age (RR 1.11)[143]; each unit increase in in utero electromagnetic exposure was linked with increased risk for asthma at 13 years (HR 1.15) [144].

DISCUSSION

The aim of this systematic review was to provide an overview of the literature describing associations between environmental exposures in early life and asthma outcomes by nine years of age. This review is mostly based on observational studies and is likely to be influenced by submission bias (where investigators do not submit papers which find no associations or challenges to current paradigms) and/or publication bias. In addition, reverse causation or confounding may explain some associations reported, e.g. postnatal exposures to antibiotics, paracetamol and perhaps pets. Moreover, observational studies cannot prove causation and most intervention studies found no effect on outcome even where studies indicated a potentially important mechanism, e.g. HDM interventions. Given these caveats, we believe that three major conclusions can be drawn. First, there was a moderately strong level of evidence (i.e. RCT, systematic review or

meta analysis) for the presence of associations between most exposures and asthma risk but the literature remains relatively deficient for exposures to infection and domestic combustion (both of which are likely to be important on a global basis). Second, where associations were present, these were of small-moderate effect size by our predefined standard. Third, we identified interactions between exposures (most commonly second hand smoke) and/or atopy which increased the risk of that exposure being associated with asthma. Given that there is no prospect of a cure for asthma, modification of the environment in early life currently offers the best hope of reducing the burden of asthma in the population and an overview of all exposures such as we present here may be of use to policy makers, health care workers and lobbying groups.

There is no single exposure which seems likely to cause asthma and even "single" exposures are invariably contaminated by other exposures. There was consistent evidence in the literature for associations between exposures to SHS, inhaled chemicals, mould, respiratory viruses, ambient air pollutants and maternal dietary components and increased asthma risk. However, each of these is a complex exposure and there was evidence of interaction between all these exposures. There is evidence that asthma risk may be related to diversity of exposure to fungus and not exposure *per se*[145] and our findings are consistent with this idea. There were inconsistent associations between asthma and exposures to pets, breast feeding and infant diet when considered separately but those intervention studies where asthma risk was successfully reduced often included modifications to some or all of these exposures. This is further evidence that asthma risk can be reduced by early exposure to an environment which is diverse in many inhaled and ingested factors common to the human environment for millennia, such as animal dander, LPS, fungi and breast milk (but not including man-made chemicals) although the exact nature of the exposure may not be relevant.

There are a number of limitations to this systematic review in addition to those already described. Firstly, in the absence of a gold standard definition of asthma, different outcomes have been used,

e.g. asthma or wheeze; these may not be interchangeable and have different associations with a given exposure. Secondly, associations reported may not be persistent: exposure to breast feeding is an example of a waning effect of a given exposure over time, presumably as current exposures modify the effect of past exposures. Thirdly, the upper age of study participants was nine years and this meant that many highly cited studies describing associations between exposure and asthma risk were not included[146]. Fourth, in our methodology we included only the latest paper from cohorts where associations may have been reported at several different ages and this will mean that transient associations are not captured; for example we have interpreted an intervention study where breast feeding was successfully prolonged as having no effect on asthma at six years[105] but the exposure was associated with reduced asthma symptoms in this cohort at ages two[147] and four[148] years. Finally, it is possible that different exposures may have a different effect on asthma risk between populations where different genetic and/or epigenetic factors may be acting.

In summary, we have reviewed the literature for associations between all environmental exposures and the development of asthma in children aged under nine years. Early life exposures to exhaled tobacco smoke, volatile organic compounds, breastfeeding, pets and many dietary factors appear to be important to the development of asthma and interactions between these exposures further increase this risk, particularly in individuals with allergic parents. Complex interventions in early life are challenging[149] but the evidence in the observational literature and from small intervention studies demonstrate that approaches using this study design may lead to stronger public health advice that such interventions are able to modify asthma risk in this age group.

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FIGURE LEGEND

Figure 1: QUOROM Statement Flow Chart.

Table I: Areas for environmental determinants of causation and exacerbation of asthma derived from stakeholder workshop.

Environmental tobacco smoke (antenatal and postnatal)
Domestic combustion (cooking, heating and candles)
Inhaled chemicals (Volatile Organic Compounds (VOC's), Chlorine, phthalates, Sulphur dioxide, Ozone)
Damp housing/ mould
Inhaled allergens (house dust mite, pets, pollens)
Air pollution
Dietary exposures (Maternal diet, breastfeeding, diet in childhood)
Respiratory virus infection
Medications (antibiotics and paracetamol)
Industrial combustion (incinerators)
Fireworks and bonfires
Vacuuming
Air conditioning or humidifiers

Table 2. Magnitude of effect of environmental exposure on respiratory symptoms including wheeze (*), asthma (†), obstructive bronchitis (¶) or atopic disease (¥) in children aged up to nine years. Details of when the exposure occurred are presented in the text and the supplemental table. ‡ indicates a randomised clinical trial, systematic review or meta analysis

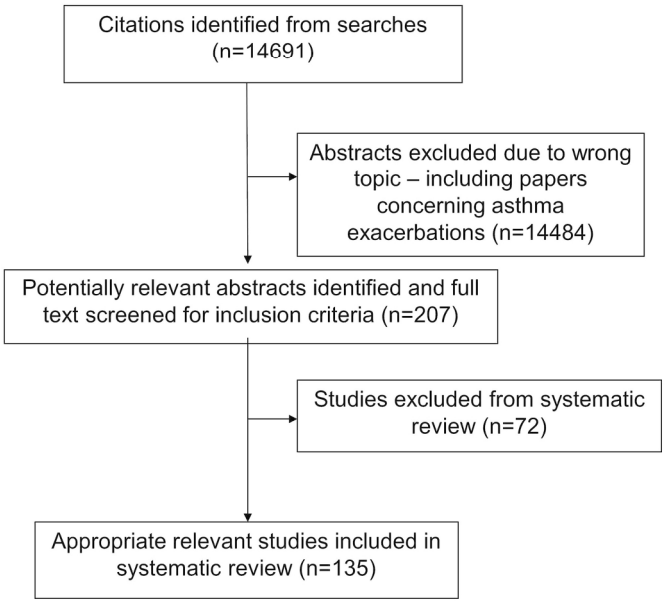
Exposure		Magnitude of effect [95 % confidence interval]
Second hand smoke	Antenatal exposure	1.7 [1.2, 2.3]‡[12] 1.13 [1.04, 1.23]* [13] 2.1 [1.2, 3.7]†[14] 1.35 [1.13, 1.62]†[15] 4.0 [1.9, 8.6]*[16] No association[17]
	Post natal exposure	1.3 [1.1, 1.6] †‡[5] 1.2 [1.0, 1.3] *[18] 2.9 [1.1, 7.2] *[17] 1.7 [1.1, 2.58]†[19]
Domestic combustion	Gas cooking	No association [21]
	Fine particulates ($PM_{2.5}$)	1.5 [1.1, 2.2] per quartile $PM_{2.5}$increase*[22]
	Detectable Sulphur Dioxide	OR 1.8 [1.1, 3.1]*[23]
	Incense	No association[24]17 [23]
	Biomass	4.3 [3.0, 5.0] † [25]
Inhaled Chemicals	VOC	1.2 [1.01, 1.4] per 10µg/m^3 increase†[26] 4.2 [1.4, 12.9]¶ [27] 2.1 [1.1, 3.9] per microg/m^3 of total MVOC *[28] 1.39 [no CI given]† [29] 2.92 [2.25, 3.75] †[30]
	Petrochemical plant	2.76 [1.96, 3.89] †Wichmann
	Chlorinated swimming pools	0.5 [0.3-0.9]†[31] No association ¥ [32]
	Other chemicals	1.7 [1.2, 2.4]* [34]33 (cleaning agents)
		1.6 [1.2, 2.1]†‡[33] (PVC)
		1.9 [1.1, 3.2]†[35](pyrene)
		0.7 [0.5, 0.9]*[36] (maternal BPA)
		1.4 [1.0, 1.9]*[36] (child BPA)
		2.8 [2.0, 3.9]†[37]and 1.7 [1.01, 2.9]*[38] (oil refinery)
Damp housing/mould		1.5 [1.3, 1.7]†‡[39] 1.4 [1.1, 1.8])*‡[40] (no association at 6-8 years) 7.1 [2.2, 12.6] †[41] 2.4 [1.1, 5.6] † [42] for exposure 2.6 [1.1, 6.3][43] per unit increase in mould index 1.8 [1.5, 22] [44] per unit increase in mould index
Multiple exposures		0.7 [0.5, 0.9]‡[48] 0.4 [0.3, 0.8]‡[49] 3.0 [1.1, 7.9] for high HDM† and 1.2 [1.1, 1.4]* per quartile LPS increase[50] 1.8 [1.02, 3.0]*increasing cockroach allergen[55] and 0.3 [0.1, 0.98]*for dog and 0.6 [0.4, 1.01]* for cat exposure[55] 2.6 [1.3, 5.4]† for high cat exposure[51] 2.7 [1.1, 7.1]† Dog and SHS, 4.8 [1.1, 21.5]† dog and elevated NO_2 [56]

		No association‡[45]‡ [46]‡ [47 52 53 54]
Inhaled allergens/particles	Pet	0.7 [0.6, 0.9])†‡cat exposure[59] 1.1 [1.0, 1.3])†‡dog exposure[59] 4.7 [1.2, 18.0])† cat exposure[61] 0.6 [0.4, 0.9]*cat exposure [62] 0.3 [0.1, 0.81]*cat exposure [63] 1.2 [1.1, 1.3]*cat exposure [64] No association‡[60 65 66]
	Other exposures	1.5 [1.1, 2.1]* highest vs lowest quartile LPS exposure [68] 1.4 [1.1, 1.7]*mouse allergen [69] 0.4 [0.2, 0.6]† feather quilt[70] 1.8 [1.0, 3.2]† number of synthetic bedding items [71] No association cockroach[52]
	HDM	No association‡[72]‡[73 74]
	Outdoor allergens	OR 3.1 [1.3, 7.4]*birthday during fungal spore season[75] OR 1.4 [1.1, 1.7]† grass pollen exposure[76] RR 1.2 [1.02-1.3]† tree canopy cover[77]
Air pollution		1.05 [1.00, 1.11]†‡ per ppm increased NO_2[78] 1.02 [1.00, 1.04]†‡ per ppm increased NO[78] 1.06 [1.01, 1.12]†‡ per ppm increased CO[78] 1.04 [1.01, 1.07]*‡ per ppm increased SO_2[78] 1.05 [1.04, 1.07]*‡ per unit increase particulates[78] 1.04 [1.01, 1.07]* per ppm increased CO[79] 1.2 [1.0, 1.31]† per 5ppb increase NO_2 [80] 2.0 [1.2, 3.6]† traffic related particles [82] 1.3 [1.0, 1.6]† higher traffic density [84] 3.1 [1.3, 7.4]† high exposure to $PM_{2.5}$ [85] No association[81]
Dietary exposures	Maternal dietary components during pregnancy	0.2 [0.08, 0.6]†‡ Mediterranean diet[86] 0.6 [0.4, 1.0]* Western diet[88] 0.6, [0.3, 0.96]* fish consumption[89] 0.8 [0.7-1.0]peanuts and 0.8 [0.7-0.8] tree nuts†[90] 1.6 [1.2, 2.0]low vegetables 1.5 [1.2, 1.8] low fruit and chocolate 1.4 [1.1, 1.7]†[91] No association fish oil[87]‡, butter and margarine[92]
	Specific nutrient intake during pregnancy	0.6 [0.4, 0.7]*‡ increased vitamin D intake[86] 0.7 [0.5, 0.9] *‡ increased vitamin E intake[86] 0.3 [0.1, 0.4] *‡ increased plasma vitamin A[86] 0.95 [0.91, 0.99]*per 10 nmol/L increase cord Vitamin D[97] No association vitamin D (plasma)[93-95] (intake)[96], dietary antioxidants[99] or folate[100] or vitamin A[101] supplements
	Breast feeding	OR 0.92 [0.86, 0.98]*‡[102] OR 1.1 [1.0, 1.2]†‡[102] 1.4 [1.2, 1.7]* never breast feeding [10302] 0.9 [0.8, 0.96]†exclusive breast feeding [104] 2.0 [1.0, 3.8]†maternal margarine intake during lactation [98] No association‡[105]
	Cows milk formula	RR 0.4, [0.2, 0.9]*‡hydrolysed vs standard[106] OR 0.3 [0.1, 1.0]*fatty acid supplementation [108] No association [109]
	Infant diet	0.4 [0.2, 0.9] for youngest vs oldest age at introduction of

		wheat †[111] 0.6 [0.4, 0.9] for early vs delayed introduction of fish[115] No association with age at introduction of solids[112,113] prebiotic supplementation‡[117]‡[118]or vitamin supplementation[119]
	Child diet	0.6 [0.4, 0.9]† full cream milk[121] 1.5 [1.04, 2.1] Western diet[124] 0.93 [0.85, 1.00] per fruit item consumption/day/week [125] 0.5 [0.3, 0.6] for highest vs lowest tertile plasma vitamin D[126] No association milk supplementation‡[120], organic food[122], dietary anti oxidant[123]
Respiratory virus infection	Respiratory infection±wheeze	0.5 [0.3, 0.9]† for infant lower respiratory tract infection [127] 9.8 [4.3, 22.0]*wheeze with rhinovirus[128] 2.9 [1.2, 7.1]†wheeze with rhinovirus [129] 2.2 [1.5-3.3]† RSV infection 6-11 months previously[130] 0.9 [0.7, 1.0]†early day care[132] No association early day care[131]
Medications	Antibiotics	1.2 [1.0, 1.5]†‡ antenatal exposure[135] 1.5 [1.3, 1.8]†‡ postnatal exposure[135] No association †‡[136]
	Paracetamol	1.3 [1.1, 1.4]†‡ [139] 1.2 [1.0, 1.4]*‡[138] No association[140]
	Other medications	1.1 [1.0,1.2] for antibiotics, 1.3 [1.1,1.6] gastroesophageal reflux treatment, 1.6 [1.1, 2.3] opiates, 1.3 [1.2, 1.4] thyroid supplements[140]
Other maternal exposures during pregnancy		2.7 [1.2, 6.0]* dietary dioxins and polychlorinated biphenyl[141] 2.3 [1.3, 4.1]* highest vs lowest BPA exposure[142] 0.7 [0.5, 0.9]* BPA exposure [36] 1.1 [1.0 1.2]* per 10% increase in DDT metabolite[143] 1.2 [1.0, 1.3] for increasing electromagnetic exposure[144]

Study	Interaction between	Magnitude of interaction
Robison[16]	Late premature delivery (<37 weeks) and antenatal SHS exposure	OR for wheeze 2.0 [1.3, 3.1] associated with prematurity and 1.1 [0.5, 2.4] with in utero SHS exposure. OR for wheeze 3.8 [1.8, 8.0] if both premature and SHS exposed
Martinez[19]	Smoke exposure from mother OR 1.7 [1.1, 2.6] for asthma by five years	OR 2.6 [1.4, 4.6] if exposed and mother ≤12 years education
Diez[27]	Redecoration Pet exposure Dampness	Redecoration associated with OR for obstructive bronchiolitis at 2 years 4.1 [1.4, 12.9]. OR 5.1 [1.6, 15.6] if also exposed to ETS or pets
Jung[35]	Pyrene exposure Atopy	High exposure was associated with increased risk for asthma 1.9 [1.1, 3.2] and this was increased to 2.9 [1.8, 5.7] among non atopic children
Carlsten[56]	Dog exposure SHS High NO_2	No association with dog exposure *per se*. OR 2.7 [1.1, 7.1] for dog and SHS. OR 4.8 [1.1, 21.5] for dog plus high NO_2
Karmus[57]	Recurrent lower respiratory tract infection SHS	OR 2.5 [1.8, 3.4] for asthma at ages 4 and 10 years. OR 3.1 [1.8, 5.2] with antenatal exposure to products of tobacco smoke
Melen[61]	Smoke exposure Pets Window pane condensation	OR for 1, 2 and 3 exposures (compared to none) were 1.1, 4.4 [1.0, 18.6] and 10.8 [2.0, 59.6].
Celedon 2002[62]	Early cat exposure Maternal asthma	Exposure associated with reduced risk for wheeze (OR 0.6 [0.4, 0.9]) but only in those with no maternal asthma.
Trevillian[71]	Synthetic bedding Bedroom heating Recent bedroom painting	Exposure to >1 synthetic item of bedding was associated with increased asthma (OR 1.8 [1.0, 3.2]). Co exposure to room heating was associated with OR 7.1 [0.1, 23.9], recent painting OR 7.2 [2.3, 23.2].
Kim [81]	Ambient air pollution (ozone, CO, NO_2, SO_2 and PM_{10}) Previous bronchiolitis	Asthma at five years not associated with higher exposures but among bronchiolitis subset ozone exposure associated with OR 7.5 [2.7, 21.3], CO exposure OR 8.3 [2.9, 23.7], and NO_2 exposure OR 7.9 [0.97, 64.8]).
Ryan [82]	Traffic related particles (elemental carbon attributable to traffic) Domestic LPS	A positive asthma predictive index at 36 months was associated with exposure to increased levels of particles before 12 months (OR= 2.0 [1.2, 3.6]). Co- exposure to high concentrations of endotoxin increased the risk (OR=3.4 [1.3, 8.9]).
Kusel[129]	Atopy Virus positive wheezing illness	OR 3.1 [1.5, 6.4] if atopic for wheeze at 5 years. OR 3.9 [1.4, 10.5] if also wheezy illness

Table 3. Magnitude of effect of main effect on asthma aetiology and magnitude of interaction with other factor.



QUOROM Statement Flow Chart.
190x142mm (300 x 300 DPI)

Supplementary file

Table I Characteristics of included studies

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Second hand Smoke-antenatal					
Neuman A, et al [1] (2012) Europe (UK, Spain, Sweden, Denmark, Germany, Netherlands)	Meta-analysis	21,600 children included in the analysis of which 735 (3.4%) met the criteria	To assess the effect of exposure to maternal smoking only during pregnancy on wheeze and asthma	A pooled analysis was performed based on individual participant data from eight European birth cohorts. Cohort specific effects were estimated using logistic regression and combined using a random effects model.	Maternal smoking during pregnancy was associated with increased risk of parental reported wheeze in the past 12 months and asthma (at least two out of three of the following criteria: (*1*) a doctor's diagnosis of asthma ever, (*2*) parental-reported wheezing during the last 12 months according to the ISAAC core questions or (*3*) asthma medication in the last 12 months) at 4 and 6 years - OR 1.4 [1.1, 1.8] and 1.7 [1.2, 2.3] respectively.
Jedrychowski et al. [2] (2009) Poland2009	Longitudinal	Children (n= 505, 468 responses) followed to the age of 2 years	To establish the pattern of prenatal environmental risk factors (ETS and particulate matter) related to the onset of wheezing phenotypes and severity of respiratory illness in early childhood.	Health and sociodemographic data collected from pregnant mothers . Children were followed up every three months to gather data on their respiratory symptoms and exposure to ETS.	Prenatal ETS exposure was associated with increased risk of wheeze (RR 1.1 [1.04, 1.23]. Other risk factors identified were maternal atopy and an inverse association with length of baby at birth.
Lannero et al.	Longitudinal	Children (n=4089,	To assess the possible	Data were collected for	Maternal smoking during pregnancy: positively

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
[3] (2006) Sweden	study	3791 total respondents) followed from birth to two years of age	effects of exposure to cigarette smoke in utero on lower respiratory disease in children up to two years of age.	maternal smoking during pregnancy, breastfeeding, parental smoking after birth, health of parents and any wheezing, recurrent wheezing and doctor diagnosed asthma in the children.	associated with asthma (OR 2.1 [1.2-3.7]).
Jaakkola et al. [4] (2004) Finland	Longitudinal	58841 (56632 total respondents) children followed for 7 years	To examine the relationship among maternal smoking in pregnancy and development of asthma in childhood.	Data collected for child's health and maternal smoking during pregnancy.	Maternal smoking during pregnancy: positively associated with risk of asthma in first seven years (OR 1.4 [1.1, 1.6]). Asthma was defined on the basis of at least 1 hospitalization due to asthma , at least 1 entitlement to free medication due to asthma or at least 1 entitlement to special care support due to asthma before the age of 7 years
Robison et al [5] (2012) USA	Longitudinal	1794 (1448 respondents) children	To investigate the interplay between exposure to tobacco smoke and prematurity in the aetiology of wheeze	Details of exposure to tobacco smoke and gestation at birth were gathered by questionnaire. Children were followed for a mean of 3.1 years and details about recurrent wheeze (≥ 4 episodes documented by physician)	Children with recurrent wheeze were more likely to have been born prematurely (average gestational age 36.5 ± 5.0 vs 37.7 ± 3.5 $p < 0.001$). There was no significant association between tobacco exposure, either in utero (OR 1.1 [0.5, 2.4]) or post natally (OR 1.4 [0.7, 2.7]). However, tobacco smoke exposure in combination with prematurity was associated with significantly increased risk of wheeze (OR 4.0 [1.9, 8.6]).

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
				obtained.	
Second hand Smoke-postnatal					
Vork et al. [6] (2007) USA	Systematic review	38 studies including approximately 200,000 children	To review the literature on second hand tobacco smoke and development of asthma in childhood	Defined asthma as wheezy bronchitis or asthma/wheeze that was ever doctor diagnosed or by a set of symptoms that are recognized criteria for diagnosing asthma in addition to wheezing	Results showed a positive association between exposure to tobacco smoke and development of asthma (RR 1.3 [1.1, 1.6]) in children 6-18 years of age.
Haberg et al. [7] (2007) Norway	Longitudinal	22390 children from fetal life to 18months	To assess children's exposure to parental cigarette smoke during and after pregnancy as risk factors for wheeze.	Data collected from parents and children on factors such as general health, nutritional status, socioeconomic status and environmental exposures. .	Maternal smoking: independent risk factor for wheeze (RR 1.25 [1.03-1.29]) Postnatal paternal smoking: risk factor for wheeze independent of maternal smoking (RR 1.14 [1.04-1.24]).
Tanaka et al. [8] (2008) Japan	Longitudinal	763 children followed through pregnancy until 24 months of age	To examine the association between maternal smoking during pregnancy and postnatal exposure to ETS and development of wheeze and asthma	Data collected for age, education, income, history of asthma, eczema and pre and post natal smoking history, wheeze and doctor-diagnosed asthma in the child.	Post natal maternal smoking, but not smoking in pregnancy, was associated with increased risk of wheeze in children (OR 2.9 [1.1, 7.2]). There was no association between smoking in pregnancy and development of wheeze or asthma.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Martinez et al. [9] (1992) USA	Longitudinal	786 children enrolled before 5 years of age	To determine the relationship of parental smoking at enrolment to subsequent incidence of asthma and lung function in a random sample of children.	Data collected from parents on smoking habits, history of wheeze or chronic cough, maternal education and data on asthma in children and lung function measurement.	Children of lower socioeconomic status were at increased risk of physician diagnosed asthma if their mothers smoked (RR 2.6 [1.4-4.6]).
Hunt et al [10] (2011) USA	Longitudinal	103 infants of asthmatic mothers	To evaluate the likelihood of infant wheeze in children exposed to varying levels of tobacco smoke and inhaled particulate matter	Particulate matter concentrations were recorded in each household. Urinary cotinine was measured 3 monthly for each infant to determine exposure to tobacco smoke. Infants were followed up for 1 year and data gathered on any diagnosis of wheeze.	Levels of particulate matter > 15 $\mu g/m^3$ were associated with increased risk of wheeze (OR 4.2 [1.4, 13.0]) Elevated urinary cotinine was also associated with a borderline increased likelihood of wheeze (OR 5.1 [0.96, 27.2])
Domestic combustion (solid fuel, gas and candles)					
Willers et al. [11] (2006) Netherlands	Longitudinal	Birth cohort (n=3148)	To investigate effect of kitchen ventilation while cooking on the relationship between gas cooking, combustion product dispersal and	Data collected for respiratory and allergic symptoms. Data was collected on gas cooking and kitchen ventilation.	Gas cooking was associated with nasal symptoms in four year olds but not with wheeze or asthma.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			respiratory outcomes in children.		
Jung et al [12] (2012) USA	Longitudinal	Children aged 5-7 (n = 262)	To evaluate the relationship between exposure to urban fine particulate matter and soot-black carbon and new onset wheeze	Integrated residential measurement of fine particulate matter and soot-black carbon was undertaken for 2 weeks in summer and 2 weeks in winter. Children were followed up for a 3 year period	Significant association was found between exposure to fine particulate matter ($PM_{2.5}$) and development of wheeze (RR 1.5 [1.05, 2.2] per quartile increase in exposure). Association was also seen between soot-black carbon exposure and development of wheeze but this was not significant (RR 1.4 [0.96, 2.1])
Yeatts et al [13] (2012) UAE	Cross sectional	628 households including 253 children and 330 adolescents	To evaluate the possible link between health problems including wheezing and asthma and exposure to indoor air pollutants	Passive air samplers were used to detect indoor air pollutants over a 7 day period. Health information was gathered by interview.	Participants in households with detectable SO_2, NO_2, and H_2S were twice as likely to report doctor-diagnosed asthma. Participants in homes with detectable SO_2 were more likely to report wheezing (OR 1.8 [1.05, 3.1]) and speech-limiting wheeze (OR 3.5 [1.06, 11.7]). $NO_2$and H_2S were also associated with increased risk for wheeze.
Padhi et al [14] (2008), India.	Case-Control	Children (1505) 5-10 years old living in 750 households (cases n=755; control n=750))	To determine the association between household use of biomass fuel for cooking and prevalence of asthma.	Questionnaire data collected for respiratory symptoms, household characteristics. Lung function measurements carried out.	Exposure to cooking smoke was significantly associated with doctor diagnosed asthma (OR 4.3 [3.0, 5.0]).

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Abdul Wahab et al [15] (2007), Qatar.	Case-control	Cases (n=100) mean age 4.31 SD 3.48, controls (n=100) mean age 4.37 SD 3.65	To determine whether exposure to environmental incense may contribute to the occurrence of asthma in Qatari children.	Data collected on past exposure to Arabian incense, family history of asthma, allergic rhinitis, atopic eczema and diagnosis of asthma.	Children exposed to incense were no more likely to have asthma (OR 0.9 [0.6, 1.2]).
Inhaled chemicals					
VOCs					
McGwin et al[16] (2011) USA	Meta analysis	7 studies	To review the possible link between formaldehyde exposure and childhood asthma	Data were extracted from the studies found and pooled in a meta analysis	Increase in formaldehyde exposure of 10µg/m^3 was associated with increased prevalence of asthma (OR 1.17 [1.01, 1.36), however definitions of asthma varied between studies.
Diez et al. [17] (2003) Germany	Longitudinal	Children (n=186) followed to 2 years of age.	To study the influence of redecoration on the occurrence of obstructive bronchitis in one and two year old children.	Data were collected at birth and at age 1 and 2 of the child. Information was gathered for redecoration of the apartments during pregnancy and first two years of life, smoking and presence of pet.	Redecoration of the home was positively associated with obstructive bronchitis (at two years OR 4.2 [1.4, 12.9]). Synergistic effects were seen with exposures to ETS and pets (OR 5.1 [1.6, 15.6]).
Kim et al. [18] (2007)	Cross sectional	1014 children from primary schools, median age 9	To study association between moulds, bacteria, MVOC (volatile	Data was collected on construction materials and ventilation. Samples were	MVOC and plasticizer concentrations were correlated r=0.5, p<0.01. MVOC and plasticizers were associated with an increased risk for any asthma (mean increased

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Sweden		(range 5-14, SD 2.0)	organic compounds of microbial origin), formaldehyde and selected plasticizer compounds in relation to doctor diagnosed asthma.	obtained to detect MVOC's, plasticizers and formaldehyde.	risk for asthma 2.1 [1.1, 3.9] per microg/m^3 increase in MVOC.
Rumchev et al. [19] (2002) Australia; Rumchev et al. [20] (2004) Australia	Case-control	Children 6months-3 years old, cases n=88, controls n=104 Cases were children diagnosed with asthma.	To determine whether early exposure to higher levels of indoor pollutants especially formaldehyde predisposes children to asthma.	Information collected for respiratory symptoms, skin prick tests carried out, formaldehyde levels estimated within the child's bedroom and living room.	Greater formaldehyde exposure during summer months. Those exposed to levels ≥ 60 µg/m^3 had an increased risk of asthma (OR 1.39, confidence intervals not provided). Cases were exposed to significantly higher levels of VOCs ($p<0.01$) especially benzene (OR 2.9 [2.25, 3.75]), ethyl benzene (OR 2.54 [1.16-5.56]) and toluene (OR 1.84 [1.41-2.41]).
Chlorine					
Font-Ribera et al. [21] (2011) Spain	Longitudinal	Children (n=5738) followed from birth to 7 years of age	To examine whether swimming in infancy and childhood was associated with asthma at age 7.	Data on swimming were gathered at regular intervals up to age 7 years. Other data gathered were information on wheezing, asthma asthma medication and potential confounders. Spirometry was carried out	Children with a high versus low cumulative swimming pool attendance from birth to 7 years had a reduced risk for ever (OR= 0.88 [0.56,1.38]) and current (OR 0.50 [0.28-0.87]) asthma.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
				from 7 to 8 years of age.	
Schoefer et al. [22] (2008) Germany	Longitudinal	Children (n=2192) followed from birth to 6 years of age	To assess whether early swimming pool attendance could be related to higher rates of asthma	Questionnaire data were gathered on socioeconomic status, medical history, lifestyle factors, information on first swimming pool attendance and doctor diagnosed asthma.	Early swimming pool attendance was not significantly associated with higher rates of atopic disease including asthma (OR 1.42 [0.65, 3.10]).
Henderson et al. [23] (2007) UK	Longitudinal	Children birth to 7 years of age (n=7162).	To assess effects of maternal use of domestic chemicals during pregnancy on wheezing and lung function.	Data collected for wheezing and household chemical exposure. Composite household chemical exposure (CHCE) score was determined.	Increased CHCE score was associated any reported wheezing: early (<18 months) OR 1.4 [1.1,1.8], intermediate (18-30 months) OR 1.4 [1.0,2.1] and late-onset (>30 months) OR 1.7 [1.2-2.4].
Other inhaled chemicals					
Jaakkola et al. [24] (2008) UK	Systematic Review	From the studies reviewed seven studies were in children age range 0-12 years of age	To review the evidence for the role of exposure to phthalates from PVC products in the development of asthma and allergies.	Seven studies in children consisted of cohort, cross sectional and case-control studies.	Presence of PVC materials in the homes: increased risk of asthma and allergy (OR 1.55 [1.2-2.1]), although definitions of asthma varied between studies
Jung et al [25]	Longitudinal	Dominican or African-American	To assess associations between exposure to	Personal air monitoring occurred for a 48 hour	High pyrene exposure was associated with increased incidence of asthma (OR 1.9 CI 1.13 – 3.2) There was

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
(2012) USA		children (n= 354)	polycyclic aromatic hydrocarbons (pyrene and non-volatile PAHs) and development of asthma	period prenatally and for a 2 week period when the children were 5-6 years old; rates of diagnosis of asthma and use of asthma medication at 5-6 years of age were ascertained by questionnaire	no association between non-volatile PA H exposure and asthma
Donohue, KM et al[26] (2011) USA	Longitudinal Study	568 pregnant women followed up until children were 12 years of age	To determine whether BPA exposure is associated with increased risk of physician diagnosed asthma	Maternal spot urine samples were collected during the third trimester of pregnancy and from children at ages 3, 5 and 7. BPA urinary concentrations were measured.	Urinary BPA concentrations at ages 3, 5 and 7 were associated with increased odds of asthma. (OR, 1.5 [95% CI, 1.1-2.0], P = .005; OR, 1.4 [95% CI, 1.0-1.9], P = .03; and OR, 1.5 [95% CI, 1.0-2.1], P = .04 respectively. Prenatal urinary BPA concentrations were inversely associated with wheeze at 5 years.(OR 0.7 [0.5, 0.9] per
Wichmann et al. [27] (2009) Australia	Cross sectional	Children (n=1212) 6-12 years old	To determine the effects of exposure to petrochemical pollution on the respiratory health of the children.	Data on children's health collected using questionnaires, measurements carried out for particulate matter and volatile organic compounds.	Living near a petrochemical plant: increased risk of having a diagnosis of asthma (OR 2.76, 95% CI 1.96-3.89) and asthma exacerbations (OR 1.88, 95% CI 1.25-1.83).
Rusconi et al[28]	Case control	489 6-14 year olds	To compare the	Parents completed surveys	Weekly average concentrations of sulphur dioxide,

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
(2011) Sardinia			prevalence of asthma in an area polluted by an oil refinery with that in a non-polluted area	on the respiratory health and risk factors of their children. Concentrations of pollutants in each area were estimated. 12-14 year olds completed spirometry and levels of pollutants in nasal mucosa were also measured	nitrogen oxide and benzene were considerably higher in the area around the oil refinery than in the control area. Children living in the polluted area had higher levels of wheezing symptoms (PR 1.70 CI 1.01 - 2.86),decreased FEV_1 (-10.3%CI -15.0 - 6.0%) and FEF_{25-75} (-12.9% CI -20.7 -4.3%), increased FE_{NO} (+35% CI 11.7 - 80.1%) and increased in MDA-dG concentrations (83% CI 22.9% - 174.1%).
Damp housing, mould					
Tischer et al[29] (2011)	Systematic Review	61 observational studies included in the systematic review	To conduct a systematic review to investigate the association between domestic mould and mould components and asthma in children.	Data from 61 observational studies was included in this systematic review. Meta analyses of the effects of visible mould exposure on allergic health outcomes were performed and findings were evaluated according to the Bradford Hill criteria for evidence of causation.	Visible mould was positively associated with asthma (OR 1.49, 95% CI 1.28-1.72).
Tischer et al. [30] (2011)	Meta Analysis	Data from 8 European Birth cohorts	To investigate whether reported mould or dampness exposure in early life is associated with the development of	Data from 31742 children was analysed. Information on exposure to mould and dampness and health outcomes was available from	Exposure to visible mould and /or dampness during first two years of life was significantly associated with reported wheeze in meta analyses of four cohorts (0-2 years: OR 1.39, 95% CI 1.05-1.84) and associated with physician diagnosed asthma later in childhood in six

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			allergic disorders in children from eight European birth cohorts.	parental questionnaires.	birth cohorts (6-8 years: OR 1.09, 95% CI 0.90-1.32).
Iossifova et al. [31] (2009) USA	Longitudinal	Children (n=483) followed up to 3 years of age.	To examine how exposure to mould and (1-3)-β-D-glucan in infancy predicts the risk of future asthma.	Data were collected for home characteristics, Dust samples and tape samples were gathered. Infants were tested for allergen sensitization.	Presence of high visible mould (OR 7.1, 95% CI 2.2-12.6) and maternal smoking (OR 4.4, 95% CI 1.7-11.6) resulted in significantly higher scores on the Asthma Predictive Index, suggesting increased risk of developing asthma in future.
Jaakkola et al. [32] (2005) Finland	Longitudinal	Children (n=1984) 1-7 years old	To assess the independent and joint effects of parental atopy and exposure to moulds in homes and development of asthma.	Data on health indicators and exposure to mould (presence of odour, moisture, visible mould and water damage).	Presence of mould in the house: increased the risk of development of (doctor diagnosed) asthma (RR 2.44, 95% CI 1.07-5.60) independent of parental atopy.
Reponen et al[33] (2011) USA	Longitudinal	176 children followed up to age 7	To determine whether mould exposure at 1 or 7 years of age was associated with increased risk of asthma at age 7.	Household mould was assessed at 1 and 7 years using DNA analysis to calculate Environmental Relative Mouldiness Index (ERMI). Parents completed a questionnaire on asthma symptoms and children also	Children living in a high ERMI household at age 1 had an increased risk of asthma symptoms at the age of 7 compared to children living in low ERMI households at age 1 (OR 2.6 [1.1, 6.3]). However, living in a high ERMI household at age 7 was not associated with increased risk of asthma symptoms at age 7.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
				underwent spirometry.	
Reponen et al. [34] (2012) USA	Longitudinal study	289 children followed from birth to 7 years of age	To assess the relationship of early exposure to specific moulds on the development of childhood asthma.	Dust samples were gathered from homes of the children at 8 months of age and children were followed up at 7 years of age to collect data on lung function tests, diagnosis of asthma, home characteristics, exposure to cigarette smoke, skin prick tests and other demographic characteristics.	Asthma was diagnosed in 24% of children at age 7 years. Exposure during infancy to three mould species common to water damaged buildings was associated with childhood asthma at 7 years of age (RR 1.8 [1.5, 2.2]).
Indoor inhaled allergens – multiple exposures					
Marks et al. [35] (2006) Australia	Longitudinal study	Children (n=616) with family history of atopy followed to 5 years of age	To examine HDM avoidance and dietary fatty acid modification implemented throughout the first five years of life as interventions to prevent asthma	Children grouped into HDM avoidance and control and dietary modification or control. HDM avoidance was achieved through physical and chemical methods. Dietary modification constituted increasing proportion of long chain polyunsaturated fatty acids	There was no difference between the groups for onset of asthma.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
				in the diet.	
Arshad et al. [36] (2007) UK	RCT, longitudinal intervention study, Intervention period 1 year, children followed up to 8 years of age.	Children in high risk category (n=120, Intervention 58, Control 62)	To evaluate the effect of reduction in food and house dust mite allergen exposure in infancy in preventing asthma and allergy.	Intervention group infants were either breast fed with mother on low allergen diet or given hydrolyzed formula. Exposure to HDM was reduced by use of acaricide and mattress covers. Development of allergic diseases and sensitization assessed at ages 1, 2, 4 and 8 in all children.	Risk of asthma was significantly reduced in the intervention group during the first 8 years of life (OR 0.24, 95% CI 0.09-0.66, p=0.005).
Maas et al [37] (2011) Netherlands	RCT	443 children with a family history of allergic asthma	To determine whether an intervention aimed at reducing exposure to tobacco smoke, inhaled allergens and food allergens and increasing breastfeeding rates decreased rates of asthma in genetically susceptible children	Parents in the intervention group received an intervention aimed at reducing exposure to tobacco smoke and various allergens shortly before their child was born. Control group received standard care.	Although exposure to dust mites, dog and cat dander was reduced in the intervention group, there was no difference in prevalence of physician diagnosed allergic asthma at age 6 (OR 1.01 CI 0.58 – 1.76)
Dotterud et al. [38] (2013)	RCT	1374 (responders) women at first	To examine the impact of an intervention	Families in the intervention arm were given advice on	There was reduced parent reported asthma in the intervention group (OR 0.68 [0.52, 0.90]). The number

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Norway		ante-natal check-up (intervention; followed until 2 years post-natal) and 4780 women 2 years post-natal (group)	recommending increased consumption of n-3 PUFAs, decreased parental smoking and decreased household dampness on development of childhood asthma	increased n-3 PUFA consumption, smoking cessation and decreasing household dampness. n-3 PUFA consumption, smoking rates and household dampness were assessed at baseline and 2 years postnatally. Asthma rates in children were compared with rates in children of mothers not subject to these interventions.	needed to treat to benefit was 53. No reduction in wheeze between groups.
Chan-Yeung et al. [39] (2007) USA	RCT	545 children with at least one first degree family member with asthma. 469 assessed at 7 years	Antenatal and postnatal reduction of HDM, SHS and pets. Promotion of breast feeding and delayed weaning to solds	Pet exposure and maternal smoking was not changed by the intervention. Intervention was associated with reduced HDM, prolonged breast feeding and delayed weaning.	Risk for asthma reduced in intervention group (OR 0.44 [0.25, 0.79])
Celedon et al. [40] (2007) USA	Longitudinal	Children (n=440) followed from birth to 7 years of age	To examine the relation between exposure to dust mite allergen and endotoxin at age 2-3 months and asthma and	Data was collected on demographic and health indicators, environmental exposures, use of tobacco and samples were collected	Exposure to high levels of dust mite allergen (≥10µg/g) was associated with increased risk of physician-diagnosed asthma at 7 years of age (OR=3.0, 95% CI 1.1-7.9) Exposure to endotoxins in the highest quartile was associated with persistent wheeze (episodes at <3

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			wheeze in high risk children.	for dust from baby's bed and bedroom floor and family room.	and 6-7 years) (OR=3.5, 95% CI 1.3-9.8, p<0.05, p for trend <0.05).
Torrent et al. [41] (2007) UK and Spain	Longitudinal study	Children (n=1182) followed from before birth to 6 years of age.	To assess the role early life exposures to Der p1 and Fel d1 on the inception of sensitization and asthma.	Data was collected for details on pregnancy and samples were gathered for cord blood, dust, ambient NO2 and blood. Skin prick tests for mother and child. Yearly questionnaire data included details on respiratory symptoms, diagnosis, household environment, exposure to pets, tobacco smoke, cooking and heating appliances.	Exposure to Der p1 early in life was not related to asthma or persistent wheeze at 6 years of age. There was a significant association between cat allergen exposure and diagnosis of asthma OR=2.6, 95% CI 1.27-5.37.
Finn et al. [42] (2000) USA	Longitudinal	Children (n=114) followed from birth to 2 years of age.	To determine whether the levels of cockroach, house dust mite and cat allergen in the home during infancy were associated with allergen specific lymphocyte	Data collected for sociodemographic and health variables. Dust samples were collected at 3 months of age for various allergens. Blood samples obtained for allergen specific	No associations between exposures and wheeze at 2 years reported.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			proliferation in later life.	lymphocyte proliferation.	
Brussee et al. [43] (2005) Netherlands	Longitudinal	Children (n=1127) followed until 4 years of age	To investigate the effect of allergen exposure at 3 months of age on the development of sensitization, wheeze and physician diagnosed asthma in the first 4 years of life in a birth cohort of children with and without an atopic mother.	Data were collected for symptoms of wheeze, physician diagnosed asthma and samples were collected from child's mattress for exposure to HDM, cat and dog allergens.	A positive association was observed between exposure to cat allergen and persistent wheeze in total study population (OR=2.31, 95% CI 0.98-5.46, p<0.10) and exposure to dog allergen and persistent wheeze in children with a non atopic mother (OR=2.50, 95% 0.92-6.80, p<0.10).
Lau et al. [44] (2000) Germany	Longitudinal	939 children followed up to age 7 years	To assess the relevance of mite and cat allergen exposure for the development of asthma up to 7 years of age.	Newborns in the cohort followed up with data collected at various stages for food and inhalant allergens, indoor allergen exposure and interviews by paediatrician.	Sensitization to indoor allergens was associated with doctor diagnosed asthma, parents report of wheeze and increased bronchial responsiveness. However there was no relation between early exposure and prevalence of asthma or wheeze.
Litonjua et al. [45] (2002) USA	Longitudinal	Children (n=226) median age 2.87, range (1.10-4.99)	To investigate the longitudinal effects of exposure to house dust endotoxin (HDE), allergen levels and presence of dog in the home on	House dust samples were collected during infancy. Data were gathered for home characteristics, environmental exposures, demographic and socio-	When all were considered, increasing cockroach allergen exposure was positively associated with wheeze by age 5 years (1.8 [1.02, 3.0]) and presence of a dog and higher concentrations of cat allergen exposure were associated with reduced wheeze risk (OR 0.3 [0.1, 0.98] and 0.6 [0.4, 1.01]. In the

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			wheezing in young children over a 4 year period.	economic characteristics and wheeze in the past year for the participants.	multivariable model, exposure to LPS was not associated with wheeze at 5 but an association was present for wheeze at 2 years.
Carlsten et al. [46] (2010) Canada	Longitudinal Study	380 children recruited at birth, 184 assessed at 7 years of age	To evaluate the effect of combined early exposure to dog allergen and indoor nitrogen dioxide or environmental tobacco smoke on asthma and bronchial hyper reactivity in a high risk birth cohort.	Perinatal environmental tobacco smoke exposure was measured using cord blood cotinine. Data were also gathered for atopy, nitrogen dioxide and urinary cotinine in the first year. At 7 years of age children were assessed for asthma and bronchial hyper reactivity.	Coexposure to elevated dog allergen and nitrogen dioxide (OR 4.8, 95% CI 1.1-21.5) or dog allergen and environmental tobacco smoke (OR 2.7, 95% CI 1.1-7.1) increased the risk of physician diagnosed asthma relative to having neither such exposure.
Inhaled allergens - pets					
Lodge et al. [47] (2012)	Systematic review of longitudinal studies	9 longitudinal studies	To conduct a systematic review of longitudinal studies in urban environments to explore the relationship between cat and dog exposure in the perinatal period and subsequent asthma.	A qualitative synthesis of the nine studies was carried out. Data were extracted for a number of variables such as exposure variables, population type, family allergy history.	The findings suggest that for children without a family history of allergy, owning a dog was protective against the development of allergic disease. No overall effect size was presented
Takkouche et	Systematic	32 Studies	To examine the		Exposure to cats reduced the risk of physician

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al. [48](2008) Spain	review		association between exposure to furry pets and asthma.		diagnosed asthma (RR 0.72, 95% CI 0.55-0.93). whilst exposure to dogs increased risk (RR 1.14m 95% CI 1.01-1.29)
Lodrup Carlsen et al. [49] (2012)	Meta-analysis	11 European Birth Cohorts children 6-10 year old	To examine the associations between pet keeping in early childhood and asthma in children aged 6-10 years.	Data from birth cohorts analysed for pet ownership and current asthma at 6-10 years of age	There was no association observed for furry and feathered pet keeping in early years of life and asthma (at least 2 of doctor-diagnosed asthma ever; asthma symptoms/wheezing in past 12 months (according to the International Study of Asthma and Allergy in Childhood); using asthma medication in past 12 months) in school age. Asthma comparing cat ownership with no pets (10 studies 11489 participants: OR 1.00, 95% CI 0.78-1.28) and dog ownership with no pets (9 studies 11433 participants: OR 0.77, 95% CI 0.58-1.03).
Melen et al [50] (2001) Sweden	Longitudinal	181 children aged 1-4 years (from cohort of 193)	To relate exposure to pets and other environmental factors at age 1-4 years to asthma outcomes	Dust collected and analysed for cat and dog allergen. Exposure to SHS and window pane condensation were ascertained from questionnaire	OR for 1, 2 and 3 exposures (cat allergen, SHS and window pane condensation, compared to none) were 1.11, 4.38 [1.03, 18.6] and 10.8 [1.97, 59.6].
Celedon et al. [51] (2002) USA	Longitudinal	Children (n=448) followed up to 5 years of age.	To examine the association between exposure to pets and asthma and wheezing in a	Questionnaire data was gathered for any pets in the house, history of wheezing or whistling in the chest.	Among children whose mother had no history of asthma, exposure to cat allergen of at least 8 µg/g at the age of 2-3 months was associated with a reduced risk of wheezing between 1-5 years of age (RR=0.6,

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			birth cohort of children whose mothers or fathers had a history of atopy.	Dust samples were collected from the household to test for cat and dog allergen.	95% CI 0.4-0.9). However this was not the case in children whose mothers had a history of asthma.
Perzanowski et al. [52] (2008) USA	Longitudinal	242 children followed up to 5 years of age (blood obtained in 323 at two yers)	To evaluate the relationship between cat ownership and development of early sensitization and wheeze.	Questionnaire data were gathered for sociodemographic and health indicators from birth to 5 years of age. Serum levels of anti- cat IgE and anti-Fel d IgG antibodies were measured.	Cat ownership was a risk factor for development of anti-cat IgE by 2years of age (RR 6.4, 95% CI 1.9-22) but not between years 2-5 (RR 0.88, 95% CI 0.24-2.3). Cat ownership was inversely related to current wheeze at 5 years (RR 0.26, 95% CI 0.083-0.81).
Brunekreef et al. [53] (2012) Netherlands	Longitudinal	206,332 children (aged 6–7 years))	To determine the relationship between cat or dog ownership and development of allergic symptoms	Parents answered questionnaires asking whether they had had a cat or dog in their home in the past year or during their first year of life. They were also asked questions regarding current symptoms allergic symptoms, including wheeze.	Cat ownership in the first year of life was associated with increased risk of current wheeze (OR 1.17 CI 1.09 – 1.26) and ever having wheezed (OR 1.12 CI 1.04 – 1.21) There was no significant association between current cat or dog ownership or dog ownership in the first year of life and wheeze.
Sandin et al. [54]	Longitudinal	Children (n=1228)	To assess the	Questionnaire data was	There was a positive but not significant association

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(2004) Sweden		followed to 4 years of age	development of different wheezing phenotypes during the first 4 years of life in relation to heredity and early pet keeping.	collected for living environment, exposure to ETS, pets, family history of atopy, breast feeding, infectious diseases and antibiotics.	between wheezing and pet ownership and family history of atopy. However an inverse association was observed between pet ownership in the first year of life and risk of late onset wheezing at 4 years of age (dog keeping OR 0.4, 95% CI 0.2-1.0).
Kerkhof et al[55] (2009) Netherlands	Longitudinal	Children (n=2951) followed up to 8 years of age	To study prospectively the effects of pets at home on development of asthma from birth up to 8 years of age.	Data was collected on allergic symptoms in the child, pets at home and potential confounders during last trimester, at three months of age and yearly around the birthday of the child until 8 years of age.	A cat decreased the risk of HDM sensitization at age 8 , however there was no significant effect on incidence of asthma
Karmaus et al [56] (2008) UK	Longitudinal	Children (n=1456) followed up to 10 years of age	To characterize the joint effects of maternal smoking, breastfeeding for at least three months and recurrent lower respiratory tract infections on childhood asthma.	Data were collected after birth and at ages 1, 2, 4 and 10 years. Information was obtained from birth records and questionnaires on breastfeeding, respiratory infections, smoking history. Skin prick tests were carried out at age 4 and 10 years.	The three risk factors maternal smoking, breastfeeding for less than three months and recurrent lower respiratory tract infections together increased the risk of asthma at age 4 and 10 years (RR 3.1, 95% CI 1.84-5.23).

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Inhaled allergens – lipopolysaccharide/farm exposure					
Genuneit [57] (2012)	Systematic review with meta analysis	Systematic review of 39 studies, including 29 studies involving children	To determine the risk of exposure to farming environments and development of asthma and wheeze in rural populations	Results were described for childhood and adulthood studies.	Results for the childhood studies showed statistically significant combined estimates OR 0.75 indicating a 25% reduction in risk of developing asthma among exposed compared to the unexposed population.
Bolte et al. [58] (2003) Germany	Longitudinal (LISA)	Children (n=1942) followed until 2 years of age	To study the effect of early endotoxin exposure on incidence of atopic sensitization, atopic dermatitis and wheezing until the age of 2 years in infants with different risk status in terms of parental atopy.	Endotoxin measurements were obtained from mothers' mattresses. Data was collected on allergic symptoms, diagnoses of asthma and sensitization to common food and inhalant allergens was assessed by specific serum IgE.	Infants at risk due to parental atopy and exposed to high endotoxin levels had a 1.8 fold increased risk of repeated wheeze (OR 1.52, 95% CI 1.08-2.14 comparing highest and lowest exposure quartiles).
Phipatanakul et al. [59] (2008) USA	Longitudinal	Children (n=498) followed from birth to 7 years of age.	To examine the relationship between mouse allergen exposure and wheezing and asthma in first seven years of life.	Questionnaire data were gathered for home environment, atopy related symptoms, dust samples were collected from bedroom, baby's bed, kitchen and living room.	Current mouse exposure was associated with an increased risk of wheeze during the first seven years of life (OR 1.4, 95% CI 1.13-1.70, p=0.002)

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Nafstad et al.[60] (2002) Norway	Longitudinal	Children (n=2531) followed from birth to 4 years of age	To explore the association between early life exposure to feather bedding and risk of developing asthma in childhood.	Data were collected for respiratory symptoms at baseline and follow up contacts with the study subjects. Information was collected for type of quilt, family history of atopy, demographic details, exposure to ETS, breastfeeding, pets and lower respiratory tract infections in the first year of life.	Risk of developing physician diagnosed asthma at 4 years of age was lower in children using feather quilt at 6 months of age compared to those with a non feather quilt (OR 0.38 [0.23, 0.64].
Gehring et al[61] (2012) Netherlands	RCT	1282 children	To determine whether allergen-impermeable mattress covers reduced exposure to house dust mite (HDM) allergen and to assess whether reduced HDM allergen exposure resulted in a decrease in asthma	Children were prenatally randomised to receive allergen-impermeable or placebo mattress covers or no mattress cover. Parents completed yearly health questionnaires until the children were 8 years old. Allergen levels were	The HDM allergen Der-f1 was significantly reduced in the mattress dust from the allergen-impermeable group compared to placebo (geometric means ratio 0.31 CI 0.11 – 0.88). There was no difference between the placebo and no-cover groups. There was a decrease in asthmatic symptoms at 2 years old in the allergen-impermeable cover users compared to placebo. There was no significant difference between groups in asthmatic symptoms at 8 years. Raised levels

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			symptoms.	measured in the child's mattress dust. Specific IgE to a variety of allergens, including HDM allergens, was measured at 1 and 8 years.	of HDM allergen IgE were not associated with increased risk of asthmatic symptoms.
Indoor inhaled allergens – house dust mite					
Trevillian et al. [62] (2005) Australia	Longitudinal study (THIS)	Children (n=863)	To investigate the role of infant bedding items as part of a composite bedding environment in the development of childhood wheezing.	Data were collected on parent and infant characteristics, home environment, child care factors and infant sleeping environment at 1 month.	There was a dose response relationship between exposure to increasing levels of composite bedding in infancy and risk of wheezing (as reported by parents). OR for asthma by 7 years 1.8 [1.0, 3.2] comparing more synthetic bedding versus none.
Woodcock et al. [63] (2004) UK	RCT	291 infants of atopic parents (511 sets of parents screened) 239 followed up at 3 years of age.	To determine whether HDM eradication in pet free households before and after birth reduces risk for asthma	Stringent and effective HDM reduction measures introduced before delivery. Dust samples collected and analyses in the first month	The intervention arm were not at altered risk for wheeze at 3 years of age.
Carter et al. [64] (2003) USA	Longitudinal	Children (n=97) followed from birth to 7 year of age	To determine whether exposure to higher levels of dust mite in infants increased the risk of	During first two years of life monthly bedroom dust samples were collected. Between age 6 and 7 years	There was no significant association between HDM exposure and development of asthma, although those children who were sensitised to HDM were more likely to have asthma ($P < 0.05$).

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			bronchial hyper responsiveness or asthma by age 6-7 years.	data was gathered for diagnosis of asthma, skin prick test and methacholine inhalation challenge.	
Inhaled allergens - outdoors					
Harley et al. [65] (2009) USA	Longitudinal study	Children (n=514) followed from birth to 2 years of age	To examine whether birth during seasons of elevated ambient fungal spore or pollen concentrations is associated with risk of early wheezing or blood levels of Th1 and Th2 type cells at 24 months of age.	Early wheezing in children confirmed from medical records. Blood samples obtained to measure Th1 and Th2 type cells. Ambient aeroallergen concentrations measured during the study period.	Birth in autumn to winter was associated with increased risk of early wheezing (OR 3.1, 95% CI 1.3-7.4). Higher pollen concentration was associated with an increased risk of early wheeze. Being born during the spore season increased the risk of early wheezing.
Erbas et al. [66] (2012) Australia	Longitudinal study	620 children aged 6 or 7 years of age	To examine the to higher ambient levels of pollen in the first 3-6 months of life and risk of eczema, sensitization to food and aeroallergens at two years and asthma at age 6-7 years combined.	Data were gathered from birth using telephone surveys on development of allergic symptoms, skin prick tests were carried out and information on diagnosis of asthma	Cumulative exposure to pollen concentration between 4 to 6 months was associated with diagnosis of asthma (OR 1.35, 95% CI 1.07-1.72).

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Lovasi et al. [67] (2013) USA	Longitudinal study	727 children aged ≤ 7years	To investigate the association of tree canopy cover with subsequent development of asthma	Birth cohort data were linked with tree canopy coverage within 0.25km of the prenatal address. Other data gathered included response to specific allergens and information on diagnosis of asthma from parental report	Tree canopy coverage was positively associated with diagnosed asthma at 7 years (RR 1.17, 95% CI 1.02-1.33).
Air Pollution					
Gasana et al[68] (2012) USA	Meta-analysis	19 studies	To evaluate the link between exposure to traffic air pollutants and wheeze or asthma	Data from studies looking at exposure to traffic air pollutants and development of wheeze or asthma were extracted and pooled in a meta analysis	Exposure to nitrogen dioxide (OR 1.05 CI 1.00 – 1.11), nitrous oxide (OR 1.02 CI 1.00 – 1.04), and carbon monoxide (OR 1.06 CI 1.01 – 1.12) were associated with higher prevalence of diagnosis of childhood asthma. Exposure to sulphur dioxide (OR 1.04 CI 1.01 – 1.07) and particulate matter (OR 1.05 CI 1.04 – 1.07) was associated with a higher prevalence of wheeze in children.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Rodriguez et al. [69] (2007) Australia	Longitudinal	Children (n=263) from birth to 5 years of age	To examine the relationship between exposure to outdoor pollution and symptoms associated with respiratory illness.	Data collected on respiratory symptoms, air pollution indicators	Of the air pollutants studied (Ozone, CO, NO2 and PM2.5) only CO was associated with increased parentally reported wheeze (increased risk 1.035 [95% CI 1.005, 1.066] per ppm increase.
Nishimura et al [70] (2013) USA, Puerto Rico	Longitudinal	Latino (n=3343) and African-American (n= 977) children	To investigate the effect of exposure to high levels of air pollution in the first year of life on asthma development	Residential history and local air quality data used to calculate early life exposure to air pollution.	A 5 part per billion increase in nitrogen dioxide was associated with a increase risk of physician-diagnosed asthma (RR 1.17, CI 1.04-1.31)
Kim et al. [71] (2013) Korea	Longitudinal study	1743 children mean age 6.8 years	To investigate the effect of air pollution on the development of asthma in children with past episodes of bronchiolitis.	Data available from the parental responses to the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires and allergy evaluations were conducted in the children. Recent exposure to air pollution was estimated using geographic information system.	NO association with exposure but both exposure and past episodes of bronchiolitis asthma risk was increased (ozone+bronchiolitis OR 7.5 [2.7, 21.3], CO+bronchiolitis OR 8.3 [2.9, 23.7], NO_2 OR 7.9 [0.97, 64.8])

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Ryan et al. [72] (2009) USA	Longitudinal	Children (n=624) followed to 36 months	To determine whether co exposure to traffic related particles and endotoxin has additive effect on persistent wheezing during childhood.	Air pollution measurements were obtained for exposure at home, day care centres and other places frequented by the children.	A positive asthma predictive index at 36 months was associated with exposure to increased levels of particles (elemental carbon attributable to traffic) before 12 months (OR= 2.0 [1.2, 3.6]). Co- exposure to high concentrations of endotoxin increased the risk (OR=3.4 [1.3, 8.9]).
Bernstein [73] (2012) USA	Longitudinal	700 children with at least 1 atopic parent	To evaluate the risk of developing asthma in children exposed to traffic pollution	Exposure to traffic pollution was estimated and children had an annual medical assessment until age 4	Wheezing without a cold was present in 23% of African American children exposures to stop/go traffic 14% to moving traffic and 11% to unexposed children. Proportions were 13%, 6% and5% for Caucasian children
Patel et al [74] (2011) USA	Longitudinal	593 children already enrolled in a birth cohort study	To evaluate the link between traffic density and respiratory health	Cohort were followed until age 10 with data collected on traffic density in their local area(s) and diagnosis of asthma	Children living in areas with higher traffic density were more likely to be diagnosed with asthma (OR 1.26 CI 1.01 - 1.57) Children living in a high traffic density area at age 1 were more likely to develop wheeze in later years
Carlsen et al[75] (2011) Canada	Longitudinal	184 children	To assess the risk of asthma and bronchial hyper-reactivity in children exposed to traffic-related air pollutants	Exposure to NO, NO_2, black carbon and particulate matter during birth year was estimated by land use regression. Children were followed until the age of 7 for diagnoses of asthma and	High (> 4.1µg/m^3) levels of particulate matter were associated with significant increase in asthma (OR 3.1 CI 1.3 - 7.4) and trends towards increased risk of bronchial hyper-reactivity. Similar findings were seen for NO and NO_2 but there was no increased risk seen with exposure to black carbon.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
				bronchial hyper-reactivity.	
Dietary exposures					
Maternal diet during pregnancy – food items					
Nurmatov et al. [76] (2010) UK	Systematic review	62 studies	To investigate the evidence that nutrient and food intake modifies the risk of children developing allergy.		Meta analysis of studies not possible, effect size not given. More convincing evidence for maternal fruit intake during pregnancy reducing asthma risk compared to vegetable intake. Evidence insufficient between Mediterranean diet and asthma risk. Fish exposure not included
Miyake et al. [77] (2011) Japan	Longitudinal	763 mother-child pairs	To examine the relationship between maternal dietary patterns during pregnancy and the risk of wheeze in the offspring aged 16-24months	Data on maternal dietary intake during pregnancy was assessed. Three dietary patterns were identified: 'healthy' with high intake of green and yellow vegetables, seaweed, mushrooms, white vegetables, pulses, potatoes, fish, sea products, fruit and shellfish; 'Western' included high intake of vegetable oil, salt-containing seasonings, beef and pork, processed meat, eggs, chicken and	Decreased maternal consumption of Western diet during pregnancy was associated with decreased risk of childhood wheeze. After adjustment for the confounding factors, ORs in the first, second, third, and fourth quartiles were 1 (reference), 0.72 (95% CI: 0.44–1.17), 0.52 (95% CI: 0.31–0.87), and 0.59 (95% CI: 0.35–0.98), respectively (p for trend = 0.02)

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				white vegetables; 'Japanese' is high intake of rice, miso soup, sea products and fish. Symptoms of wheeze and were based on criteria from the International Study of Asthma and Allergies in Childhood	
Romieu et al. [78] (2007) Mexico	Longitudinal	462 pregnant women enrolled and children followed from birth to 6 years of age.	To evaluate the impact of fish oil consumption during pregnancy on the incidence of asthma.	Dietary intake of women assessed by using a food frequency questionnaire. Data gathered yearly on episodes of wheezing, diagnoses of asthma, serum samples gathered for specific IgE levels and skin prick tests were carried out..	Fish intake during pregnancy was protective against atopic wheeze at 6 years of age (OR 0.55, 95% CI 0.31-0.96). An increase of fish intake from once per week to 2.5 times per week decreased the risk of wheeze at age 6 years by 82%.
Maslova et al (2012) Denmark[79]	Longitudinal	61,908 mother-child pairs	To determine whether high levels of maternal tree nuts and peanuts during pregnancy were associated with increased	Maternal tree nut and peanut consumption was estimated using a validated questionnaire. Parental questionnaires were used to determine prevalence of	Maternal intake of peanuts (OR, 0.79; 95% CI, 0.65-0.97) and tree nuts (OR, 0.75; 95% CI, 0.67-0.84) was inversely associated with asthma in children at 18 months of age. Higher tree nut intake was inversely associated with a medication-related asthma diagnosis (OR, 0.81; 95% CI, 0.73-0.90). Compared with mothers

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			risk of childhood asthma.	recurrent wheeze (>3 episodes) and 18 months of age and diagnosed asthma at 7 years.	consuming no peanuts, children whose mothers reported eating peanuts 1 or more times per week were 0.66 (95% CI, 0.44-0.98) times as likely to have asthma.
Erkkola, M et al[80] (2012) Finland	Longitudinal study	2441 children at 5yrs of age	To study the effect of maternal food consumption during pregnancy on the emergence of asthma and wheeze by 5 yrs	Data from children were analysed within the Finnish Type 1 Diabetes Prediction and Prevention Nutrition Study. Maternal diet was assessed with a validated food frequency questionnaire	Low maternal consumption of leafy vegetables ([aOR]: 1.55; 95% CI: 1.21, 1.98), malaceous fruits (aOR: 1.45; 95% CI: 1.15, 1.84), and chocolate (aOR: 1.36; 95% CI: 1.09, 1.70) were positively associated with the risk of wheeze in children. No associations were observed between maternal food consumption and asthma.
Nwaru, BL et al [81] (2012) Finland	Longitudinal Study	2441 children aged ≥ five years	To investigate the effect of maternal intact of fatty acids during pregnancy on the risk of wheeze.	Information on maternal diet was assessed by a validated FFQ and information on allergies was analysed by the International Study of Asthma and Allergies in Childhood	There was no significant association between maternal consumption of fatty acids during pregnancy and childhood wheeze.
Maternal diet during pregnancy – individual nutrients					
Nurmatov et al. [76] (2010) UK	Systematic review	62 studies	To investigate the evidence that nutrient and food intake modifies		Serum vitamin A was lower in children with asthma compared to controls (OR 0.25, 95% CI 0.10-0.40). High maternal dietary vitamin D and E intakes during

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			the risk of children developing allergy.		pregnancy was protective for development of wheeze (OR 0.56, 95% CI 0.42-0.73 and OR 0.68, 95% CI 0.52-0.88 respectively).
Dunstan et al. [82] (2003) Australia	RCT	83 pregnant mothers	To determine whether fish oil supplementation modified neonatal immune responses	Atopic mothers were randomised to placebo or fish oil supplement during pregnancy. Infants followed up at one year	No difference in respiratory outcomes between groups.
Pike, KC et al[83] (2012) UK	Longitudinal Study	860 pregnant women and their children up to 6 years	To assess the relationship between mother serum 25-hydroxyvitamin D status and asthma and wheeze phenotypes in their children at 6 years of age.	Data was collected in the 34th week of gestation and questionnaire data collated from 6, 12, 24 and 36 months and 6 years of age. Spirometery and skin prick testing was performed at 6 years of age.	There were no significant associations between late maternal 25-hydroxyvitamin D status and either asthma or wheeze at 6 years. No associations were found with either skin sensitization or lung function.
Morales, E et al [84] (2012) Spain (742)	Longitudinal Study	1724 children	Assessment of whether maternal circulation 25-hydroxyvitamin D (25[OH]D) concentrations in pregnancy were associated with a risk of wheezing and asthma in	Maternal circulating 23(OH) D concentrations were measured in pregnancy (mean gestational age = 12.6 weeks). From the age of 1 parents were asked annually if their child had a physician-confirmed history of LRTI or	There was a trend for an association between higher levels of circulating 25(OH)D in pregnancy and decreased odds of LRTI in offspring)(for cohort- and season-specific quartile Q4 vs. Q1, odds ratio = 0.67 [95% confidence interval = 0.50-0.90]; test for trend, P = 0.016) No association was found between 25(OH)D levels in pregnancy and risk of wheezing at 1 or 4

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			the offspring	wheezing. Asthma was defined as parental report of a doctor diagnosis of asthma or treatment at the age of 4-6 years	years, or asthma at age 4-6 years
Hollams, Em et al[85] (2011) Australia	Longitudinal Study	989 6 year olds and 1,380 14 year olds	To investigate associations between plasma vitamin D and allergy and asthma development in children age 6 and 14 years	Serum Vitamin D was assayed in the 6 and 14 year olds. Lung function was assessed by spirometry and BHR was assessed by metacholine challenge. Total and specific IgE were measured by ImmunoCap and subjects were considered atopic if they had any measured specific IgE ≥0.35 $kU \cdot L^{-1}$ for age 14 yearsor total IgE ≥100 $kU \cdot L^{-1}$ for age 6 years	Relationships between Vitamin D status and clinical conditions were seen only amongst males. Compared to those with sufficient Vitamin D, males without sufficient Vitamin D had an increased frequency of BHR (19.6 versus 13.3%; p=0.031) atopy (72.2versus 61.1%; p=0.003) and HDM sensitisation (50.2 versus 39.8%; p=0.007), The trends were similar or asthma (13.5 versus 9.4%; p=0.094) and poor lung function (12.5 versus 8.5%; p=0.087)
Miyake, Y et al[86] (2011) Japan	Longitudinal study	763 Japanese child-mother pairs	To investigate the relationship between maternal vitamin B intake during pregnancy and wheeze and eczema in infants ages 16-24	Data on maternal intake were assessed with a diet history questionnaire. Symptoms of wheeze were based on the criteria of the international study of	There were no significant relationships between maternal consumption of Vitamin B and folate during pregnancy and the risk of wheeze n the offspring.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			months	asthma and allergies in childhood.	
Camargo et al. [87] (2011) USA	Longitudinal	Children (n=922)	To examine the role of vitamin D in childhood respiratory health.	Cord blood levels of newborns were tested for 25 (OH) D. Details on any respiratory symptoms were collected at 3 months and 15 months and annually thereafter to 5 years of age.	Cord blood levels were inversely associated with risk of wheezing from age 3 months to the age 5 years (OR 0.95 [0.91, 0.99] for wheeze by 5 years per 10 nmol/L increase). Similar relationship was not identified for asthma.
Lumia et al[88] (2011) Finland	Longitudinal study	1798 children	To explore the association of maternal dietary FA composition during pregnancy with the risk of asthma in the offspring	Dietary intake was assessed by a food frequency questionnaire 8 months into the pregnancy and the occurrence of asthma assessed at 5 years with a modified questionnaire from the ISSAC	Low maternal intakes of α-linolenic acid [lowest quarter vs. mid-half HR 1.67 (95% CI 1.12–2.48)] and total n-3-polyunsaturated fatty acids [HR 1.66 (95% CI 1.11–2.48)] during pregnancy were associated with an increased risk of asthma in the offspring, while a low intake of arachidonic acid [HR 0.52 (95% CI 0.32–0.84)] and high intake of total saturated fatty acids [highest quarter vs. mid-half HR 0.55 (95% CI 0.34–0.90)] and palmitic acid [HR 0.51 (95% CI 0.31–0.83)] were associated with a decreased risk of asthma
Nwaru et al [89] (2011) Finland	Longitudinal Study	2441 children	To investigate the association between maternal intake of antioxidants during pregnancy and the risk of	The study was on the basis of the Finnish Type 1 Diabetes Prediction and Prevention Nutrition study, complete information on	Maternal intake of antioxidants was not significantly associated with the risk of asthma in offspring.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			asthma, rhinitis and eczema in 5 year old children	maternal food frequency questionnaire data and ISSAC- based allergic outcomes were available for 2441 children	
Martinussen et al. [90] (2011) Norway	Longitudinal	1,499 women – and their children who were followed up until the age of 6years	To assess whether maternal folic acid intake during the first trimester of pregnancy is related to asthma in the offspring by the age of 6 years	Data on folic acid use and content was collected before 24weeks of gestation, and at a month before conception through the third month of pregnancy. Asthma in the children was assessed at the age of 6years	Folic acid supplementation during pregnancy did not lead to a statistically significant decrease in asthma at 6 years of age.
Checkley, W et al[91] (2011) USA	Longitudinal Study	5,430	To examine the long term effects of Vitamin A supplementation early in life on later asthma risk	Two cohorts were enrolled in randomised Vitamin A supplementation. One cohort received Vitamin A or placebo for <16 months during their pre-school years. The second cohort was born to mothers who received Vitamin A before, during or after pregnancy. At follow-up both cohorts were asked about asthma	No difference was found between the Vitamin A supplemented and placebo groups from either trail in the prevalence of lifetime or current asthma and wheeze, [$p \geq 0.12$ for all comparisons]

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
				symptoms and spirometry was performed.	
Breastfeeding					
Brew et al (2011)[92]	Meta-analysis	31 studies	To investigate the link between any or exclusive breastfeeding and development of childhood wheeze or asthma.	Meta-analysis and subgroup analysis.	There was no association found between any or exclusive breast feeding and wheezing illness. Subgroup analysis found that breast feeding slightly lowered the odds of wheeze (pooled odds ratio 0.92 [0.86, 0.98]) but slightly increased the odds of asthma (pooled odds ratio 1.10 [1.00, 1.22]) when asthma was defined as the presence of any two of: ever diagnosed by a physician, wheeze in the last 12 months, use of asthma medication in the last 12 months and bronchial hyper-responsiveness).
Sonnenschein-van der Voort et al. [93] (2011) Netherlands	Longitudinal	5,369 preschool children	To examine the associations of breastfeeding duration and exclusiveness with the risks of asthma-related symptoms in preschool children – and to explore whether these associations are explained by atopic or	Information on breastfeeding duration and exclusiveness were obtained at 2, 6 and 12months after birth. Information on asthma-related symptoms was obtained at the ages of 1, 2, 3 and 4years.	Children who were never breastfed had increased risk of wheeze during the first 4 years of life (OR 1.44 CI 1.24 – 1.66) compared to children who were breastfed for 6 months. Children who were never breastfed, or breastfed for only 3 or 6 months tended to have asthma-related symptoms earlier than those who were breastfed for >6 months although these results did not reach statistical significance (HR 1.13 CI 0.97 – 1.32; HR 1.06 CI 0.96 – 1.17; HR 1.03 0.92–1.15).

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			infectious mechanisms		
Silvers et al. [94] (2012) New Zealand	Longitudinal	892 infants from birth to the age of 6 years	To investigate the effects of breastfeeding on wheezing and current asthma in children from 2 to 6 years of age	Breastfeeding in 1105 infants was assessed at birth and at 3, 6 and 15months-breastfeeding was assessed in two ways: 'exclusive' and 'any'. The infants were assessed for 'current asthma' or 'current wheezing' at 2, 3, 4, 5 and 6years	Exclusive breastfeeding was associated with decreased risk of asthma at 2 (OR 0.85 CI 0.76 - 0.94), 3 (OR 0.88 CI 0.80 - 0.97), 4 (OR 0.92 CI 0.84 – 1.0) and 5 years (OR 0.88 CI 0.80 - 0.96) but no significant decrease in risk of asthma at 6 years. Any breastfeeding was also associated with decreased risk of asthma at 2 (OR 0.94 CI 0.90 – 0.97), 3 (OR 0.94 CI 0.91 – 0.97), 4 (OR 0.96 CI 0.92 – 0.99) and 5 years (OR 0.98 CI 0.94 – 1.0) but no significant decrease in risk of asthma at 6 years.
Kramer et al [95] (2007) Belarussia	RCT	17046 pregnant mothers 13889 children followed up at 6.5 years	To determine whether prolonged breast feeding had a durable effect of asthma outcome	Mothers were randomised by centre to receive breast feeding promotion or standard advice	There was no difference between children who received the intervention and standard advice.
Lumia et al[96] (2012) Finland	Longitudinal Study	1798 mother-child pairs from the Type 1 Diabetes Prediction and Prevention Nutrition Study	To explore the association between maternal dietary fat and fatty acid intake during lactation and the risk of asthma in the offspring	Dietary intake was assessed by a food frequency questionnaire and the cumulative incidence of asthma assessed at 5 years with a modified questionnaire from the	The maternal use of margarines was associated with a marginally increased risk of asthma (hazard ratio (HR) for user vs. nonuser 1.96, 95% confidence interval (CI) 1.01–3.82, p = 0.047) The maternal intake of of FA and fish during lactation were not associated with the risk of asthma.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			by 5 years	ISSAC	
Infant feeding/weaning					
Ram et al [97] (2004) Netherlands	Systematic review	10 trials	To quantify the risk of asthma or wheezing in infants fed standard cow's milk based formula compared to hypoallergenic formulas.		Risk of wheezing and asthma was reduced in infants when using hydrolysed milk formulas in the first year of life. (RR 0.40, 95% CI 0.19 to 0.85) There was insufficient evidence to suggest benefits of soya based milk formula in modifying the risk of wheeze or asthma.
Morisset et al. [98] (2010) France	Randomised controlled trial	129 children from birth to the age of 24months	To determine the impact of the not-hydrolysed fermented infant formula 'HKBBST' on the incidence of allergy-like events during the first 2years of life in children at high risk of atopy	Infants were given either HKBBST (n=66) or standard infant formula (n=63), from birth until the age of 1year, and were followed at 4, 12 and 24months after birth. Skin prick tests for foods (cow's milk, hen's egg, codfish, wheat flour, soy flour and roasted peanut) and aeroallergens (dermatophagoïdes pteronyssinus, cat and dog dander, grass pollens, birch pollen and Alternariia alterna) were performed,	Use of HKBBST decreased respiratory potentially allergic adverse events(wheeze, wheezy bronchitis and spastic bronchitis) (7 vs 21%, P=0.03) at 12 months, at 24 months (13 vs 35%, P=0.01).

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
				and adverse events were recorded	
Birch et al. [99] (2010) USA	RCT	Children (n=89)	To assess the effects of Docosahexanoic acid (DHA) or Arachadonic Acid (ARA) supplementation in infancy, consistent with worldwide human milk levels on the incidence of respiratory infections and allergic illnesses through 3 years of age.	Infants were randomly assigned to receive either DHA or ARA formula. Data were gathered for episodes of allergic manifestations, respiratory illnesses during the first three years of life.	The DHA/ ARA group had significantly less chance of developing wheezing/ asthma (OR 0.32, 95% CI 0.11-0.97).
Kuo et al. [100] (2011) Taiwan	Longitudinal	679 infants who had at least 1 1st degree family member with a history of atopy. Followed from birth to the age of 36months	To investigate whether feeding a protein-hydrolysed formula (HF) in the first 6months of life decreased allergic diseases up to 36months later. This was compared to cow's milk (CM) consumption	Infants were fed with HF or CM for at least 6months via an open-label protocol, and were monitored prospectively at 6, 18 and 36months of age, to asses allergy sensitisation and allergic disease	Infants fed with HF during the first 6months of life had a no significantly reduced risk of asthma compared to CM fed infants.
Nwaru et al.	Longitudinal	3781 children from birth to the age of	To investigate the associations between the	Dietary exposures were analysed at the ages of 3, 6	Introduction of wheat, rye, oats, and barley before 5 months (OR 0.72 CI 0.44 - 1.19) or at 5 to 5 and a half

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
[101] (2013) Finland		5years	duration of breast-feeding and timing of introduction of complementary foods and the development of asthma and allergies by the age of 5years	and 12 months. Further forms were filled regarding the age at which new food was introduced. The exposures of interest were: breastfeeding, cow's milk; roots (carrots, potatoes, turnips); fruits and berries; wheat, rye, oats and barley; meat; fish; eggs; and other cereals (maize, rice, millet and buckwheat)	months (OR 0.59 CI 0.41 - 0.86) was associated with decreased risk of asthma compared to introduction after 5 and a half months. Introduction of egg before 8 months (OR 0.61 CI 0.39 - 0.94) or at 8 to 11 months (OR 0.55 CI 0.38 - 0.81) was associated with decreased risk of asthma compared to introduction after 11 months.
Virtanen et al. [102] (2010) Finland	Longitudinal	Children (n=1293)	To assess how age at introduction of different foods or food groups as well as breastfeeding during the first year of life is related to the emergence of asthma and allergic rhinitis by the age of 5 years in a cohort of children with increased HLA-DQB1-conferred risk for type 1 diabetes.	Data on infant feeding patterns was gathered suing a dietary questionnaire. At 3,6,12 and 24 months of age. Data were also collected for history and symptoms of asthma, allergic rhinitis and atopic eczema at 5 years of age.	Early age at introduction of oats was associated with a reduced risk of persistent asthma for the first tertile (HR 0.36, 95% CI 0.15-0.85) and mid tertile (HR 0.37, 95% CI 0.22-0.62) compared to the last tertile ($p<0.001$). Similar results were also observed for introduction of fish ($p<0.001$).
Mihrshahi et	Longitudinal	Children (n=616)	To examine the	Information was provided on	No association between introduction of solids before 3

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
al. [103] (2007) Australia	(CAPS Childhood Asthma Prevention Study)	followed up to 5 years of age	relationship between infant feeding practices and the risk of asthma at age 5 years.	the benefits of breastfeeding and on introduction of solids after 4-6 months. Data were collected on breastfeeding and introduction of solids during home visits. Information on allergic outcomes at 5 years of age was	months and asthma.
Zutavern et al. [104] (2008) Germany	Longitudinal (LISA)	Children (n=2073)	To examine whether a delayed introduction of solids (past 4 or 6 months) is protective against the development of asthma at the age of 6 years.	Data was collected for respiratory symptoms, feeding practices, lifestyle and environmental factors.	The results showed no association between delayed introduction of solids and risk asthma.
Kremmyda et al. [105] (2011) United Kingdom	Systematic Review	14 studies	To determine the impact of fish oil consumption on development of asthma and atopy	Systematic review of studies looking at fish oil consumption and asthma.	8 of 14 studies identified reported reduced asthma outcomes associated with fish exposure in the diet. Protective effect varied between 25% and 95%.
Kiefte-de Jong et al. [106] (2012)	Longitudinal	7,210 children, from birth to 48months	To assess whether timing of introduction of fish in the first year of life and	Timing of introduction of fish into the infant's diet was assessed at 12 and 14	Introduction of fish between 6 and 12 months was associated with decreased risk of wheezing at 48 months (OR 0.64 [CI 0.43 – 0.94]) compared to not

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Netherlands			fish consumption afterward were associated with the development of asthma-like symptoms at preschool	months. The presence of asthma-like symptoms were later assessed at the child's age of 36 and 48 months	introducing fish in the first year of life. No introduction of fish in the first year was associated with increased risk of wheeze at 48 months (OR 1.57 CI 1.07 – 2.31), as was introducing fish between 0 and 6 months (OR 1.53 CI 1.07–2.19) compared to introducing fish between 6 and 12 months. There was no association between amount of fish consumed at age 14 months and development of wheeze.
D'Vaz et al. [107] (2012) Australia	Randomised control trial	Healthy term infants of 420 allergic women – from birth to 6months	To investigate the effects of fish oil from birth until 6months of age on allergic outcomes in children at high allergic risk	Infants at high atopic risk received either a daily supplement of fish oil, or a placebo (olive oil), from birth up to the age of 6months. PUFA levels were measured in infants' erythrocytes and plasma, and their mothers' breast milk. Asthma was assessed at 12months of age.	Postnatal fish oil improved infant n-3 (omega-3 polyunsaturated fatty acids) status, but lead to no statistically significant reduction in childhood allergic disease.
Osborn et al. [108] (2012) Australia	Systematic review with meta-analysis	2 eligible studies (total of 226 infants)	To review the evidence for prebiotic supplementation in infants to prevent development of asthma		Meta analysis found no significant difference in infant asthma with the use of prebiotics although significant heterogeneity was found between studies

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Kukkonen et al. [109] (2011) Finland	RCT	1,018 children	To study the effect of probiotic treatment during the first six months of life, on airway inflammation at the age of 5years	1,018 children were given a probiotic combination plus prebiotics, or a placebo, from birth to the age of 6months. Exhaled nitric oxide (FE_{NO}) was measured in 160 children as a surrogate marker of asthma and atopy.	No significant difference in FE_{NO} was found between the probiotic treated and non-treated groups.
Milner et al. [110] (2004) USA	Longitudinal	Children (n=8285)	To determine whether early vitamin supplementation during infancy affects the risk of asthma during early childhood.	Data were collected for breastfeeding, vitamin supplementation, respiratory symptoms and food allergies.	History of vitamin use within first six months of life was associated with an increased risk of asthma in black infants (OR 1.27, 95% CI 1.04-1.56).
Child Diet					
Giovannini et al. [111] (2007) Italy	RCT	Children (n=187; Intervention n=92, control n=95)) aged 2-5 years.	To investigate whether the long term daily consumption of fermented milk containing a specific *Lactobacillus casei* may reduce the occurrence and duration of asthma	Intervention group received fermented milk whereas the control group received non fermented milk. Consumption of other products containing probiotic bacteria was forbidden. Data were	No difference was observed for asthma episodes between the groups.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
			modify the immunologic profile of pre-school children with allergic asthma.	collected for respiratory symptoms, abdominal symptoms, any other illness and use of antibiotics. Faecal samples were obtained from a subsample to test for the presence of Lactobacillus casei and immunologic blood assessment was carried out among the study subjects.	
Wijga et al. [112] (2003) Netherlands	Longitudinal	Children (n=2978)	To investigate the role of diet in the development of asthma in pre-school children.	Food frequency data gathered at two years of age. Data was collected for asthma symptoms at age 3 years.	Prevalence of wheezing and asthma at 3 years of age was lower in children who consumed full cream milk daily (3.4%) compared to those who did not (5.6%) OR=0.59, 95% CI 0.40-0.88.
Kummeling et al. [113] (2008) Netherlands	Longitudinal	Children (n=2384) followed from birth to 2 years of age.	To investigate whether early life organic food consumption was associated with the development of atopic manifestations in the first two years of life.	Data collected on organic food consumption in second year of life, history of eczema and wheeze and serum total IgE antibodies.	Wheeze not associated with consumption of an organic diet.
Patel et al. [114]	Longitudinal	Children (n=861)	To investigate whether	Questionnaire data were	There was no association between antioxidant intakes

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
(2009) UK	(MAAS)	followed from birth to 8 years of age.	dietary antioxidant intake at age 5 was related to atopy at age 5 and 8 years of age.	gathered for respiratory symptoms and dietary intake. Skin prick tests were carried out to test for allergens.	and wheeze.
Tromp et al. [115] (2011) Netherlands	Longitudinal	6,905 preschool children- followed from birth to the age of 4years	To examine whether different childhood dietary patterns are associated with respiratory symptoms in Dutch children up to 4 yrs of age.	At the child's age of 14 months (±2 months) parents were asked to complete a food frequency questionnaire. Dietary patterns were then classified as Western (associated with refined grains, soups and sauces, savoury and snacks, other fats, sugar-containing beverages and meat) or health conscious (associated with starchy foods, fruit, vegetables, potatoes, vegetable oils, fish, legumes and meat).Data on asthma-related symptoms were obtained by questions adapted from the "International Study of	High adherence to the “Western” dietary pattern was significantly associated with frequent shortness of breath (RR 1.43 CI 1.01 – 2.03) at age 2 yrs. High adherence to the “Western” dietary pattern was also significantly associated with frequent wheeze (RR 1.39 CI 1.02 – 1.89) and frequent shortness of breath (RR 1.66 CI 1.24 – 2.21) at age 3 yrs. However, the association between the “Western” dietary pattern and frequent shortness of breath at the age of 2 and 3 yrs was mainly explained by confounding variables. High adherence to the “Western” dietary pattern was also significantly associated with frequent wheeze (RR 1.70 CI 1.22 – 2.36) and shortness of breath (RR 1.44 CI 1.03 – 2.01) at age 4 yrs. However, this association was again mainly explained by confounding variables. After adjustment for total energy intake, high adherence to the “Western” dietary pattern remained significantly associated with frequent wheeze (RR 1.47 CI 1.04 – 2.07) at 3 yrs of age.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
				Asthma and Allergies in Childhood" (ISAAC) core questionnaires on asthma at the age of 2, 3 and 4 yrs.	
Willers et al. [116] (2010) Netherlands	Longitudinal	2,870 children from birth to the age of 8 years	To investigate whether asthma or atopy outcomes at 8 years of age were associated with long-term dietary exposure, and whether associations were different for consumption at early or later age	Dietary intake was collected using annual questionnaires from the age of 2 to 8years. The intakes of interest were fruit, vegetables, brown/wholemeal bread, fish, milk, butter and margarine. Early age was defined as 2-3years, and late age was defined as 7-8years. Associations between early age and late age, and long-term intake, asthma and atopy at 8years of age were calculated.	Their results showed that fruit consumption at early age was associated with reduced asthma symptoms (OR per 1 consumption day per week increase 0.93, CI 0.85–1.00). Long-term fruit intake is inversely associated with asthma symptoms (OR 0.90 CI 0.82 – 0.99). There were no consistent associations between diet and outcomes for other foods
van Oeffelen et al. [117] (2011) Netherlands	Longitudinal	Children from birth until 8years of age-n=372 in the 4year-old group, and	To investigate the cross-sectional and prospective associations between serum concentrations of	From a 'Prevention and Incidence of Asthma and Mite Allergy birth cohort', serum nutrient	There was a trend towards decreased asthma incidence in children with higher serum magnesium levels, but this did not reach statistical significance. At age 4, higher serum vitamin D levels were associated

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
		n=328 in the 8year-old group	magnesium, vitamin D, selenium and zinc, and prevalence of asthma atopy.	concentrations of magnesium and vitamin D were available for a 4yr-old subgroup and for an 8yr-old subgroup. Questionnaires about the child's asthma symptoms and corticosteroids use were answered annually, until the age of 8years.	with decreased risk of asthma at 8 years (OR for tertile 1 vs tertile 3 0.45 [0.32, 0.57]), however at age 8, higher serum vitamin D levels were associated with increased risk of asthma (OR for tertile 1 vs tertile 3 2.14 CI 0.67 – 6.82)
Infections					
Illi et al. [118] (2001) Germany	Longitudinal (MAS)	Children (n=1314) followed from birth to 7 years of age	To investigate the association between early childhood infections and the subsequent development of asthma.	Data on asthma and asthmatic symptoms were gathered from questionnaires. Information was also sought on infectious diseases in the first years of life. Blood samples were tested annually for specific IgE and bronchial histamine challenge was performed at 7 years of age.	Repeated lower respiratory tract infections showed a positive association with wheeze up to 7 years of age (OR 3.37, 95% CI 1.92-5.92). Children with two or more episodes of rhinitis before the age of one were less likely to have doctor's diagnosis of asthma (OR 0.52, 95% CI 0.29-0.92).

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Jackson et al. [119] (2008) USA	Longitudinal	Children (n=259) followed from birth to 6 years of age.	To define the relationship between specific viral illnesses and early childhood asthma development.	Nasopharyngeal mucus samples were collected at clinic visits and during acute respiratory illnesses. Nasal specimens were analyzed for respiratory viruses. Allergen specific IgE was measured for dust mite and skin prick testing was performed to test for aeroallergens.	From birth to 3 years of age wheezing with RSV was associated with an increased risk of asthma at 6 years of age (OR 2.6 [1.0, 6.3], wheezing with rhinovirus (RV) (OR 9.8 [CI 4.3, 22.0]) and wheezing with both RSV and RV (OR 10.0 [4.5, 22.2]).
Kusel et al. [120] (2007) Australia	Longitudinal	Children (n=198) followed from birth to 5 years of age	To examine the relationships between early life respiratory viral infections, atopic sensitization and development of asthma.	Data gathered on episodes of infections, samples were collected for postnasal aspirates for viral identification.	Any wheezy or febrile lower respiratory tract infection with rhinovirus was associated with a significantly increased risk of doctor-diagnosed asthma at 5 years (OR 2.9, [1.2-7.1], p=0.02).
Stensballe et al. [121] (2009) Denmark	Longitudinal	Children (twins n=8280 pairs) followed from birth to 5 years of age.	To examine the causal direction of association between RSV hospitalization and asthma.	Information from RSV hospitalization and asthma status gathered from twin registry.	Risk of asthma increased 6 to 8 fold in the 2 months following hospitalization for RSV but this risk disappeared 1 year after initial hospitalisation.
Caudri et al. [122]	Longitudinal	Children (n=3963) followed up to 8	To study the effects of day-care on development	Data gathered for sociodemographic factors,	Early day care as a proxy for respiratory infections increased the risk of wheeze up to 4 years of age but

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
(2009) Netherlands		years of age	of asthma and allergic sensitization during first 8 years of life.	health indicators and day care use.	fewer symptoms between the ages of 4-8 years. No protection was observed for asthma symptoms at 8 years of age (OR 0.99, 95% CI 0.74-1.32).
Midodzi et al. [123] (2010) Canada	Longitudinal	8499 children aged <2 years followed up to 5 years of age	To relate early life exposures to asthma outcome at five years	Questionnaire based study	Early day care attendance associated with reduced asthma risk (HR 0.85, 95% CI 0.74-0.98)
Hesselmar et al. [124] (2013) Sweden	Longitudinal study	184 children followed from birth to 36 months	To examine whether the mode by which the parents clean their infant's pacifier affects the risk of allergy development in the infant.	Data were gathered for feeding practices, weaning foods, use of and cleaning practices for the pacifiers, blood samples for allergen specific antibodies and information on diagnosis of wheeze and asthma.	Children whose parents cleaned their pacifiers by sucking it were less likely to have wheeze (OR 0.12, 95% CI 0.01-0.99) at 18 months.
Alcantara-Neves et al. [125] (2012) Brazil	Longitudinal study	1128 children 4-11 year old	To investigate the effect of single or multiple infections on atopy and wheeze in urban children from Latin America.	Data were gathered for specific IgE and skin prick tests, wheezing, infections by 8 pathogens using serology and stool examination.	Isolated infections or pathogen burden were not associated with the prevalence of atopic or non atopic wheeze.
Medications					

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Antibiotics					
Murk et al. [126] (2011) USA	Systematic review	20 studies	To evaluate the evidence of association between antibiotic exposure during pregnancy or in the first year of life and risk of childhood asthma.		Results from the review supported the increased risk associated with use of antibiotics during pregnancy (odds ratio 1.24 [1.02, 1.50]) or infancy (odds ratio 1.52 [1.30, 1.77]) but authors acknowledge the role played by reverse causality and protopathic bias.
Penders et al. [127] (2011) Netherlands	Systematic review	21 longitudinal studies	To review longitudinal studies and describe how outcome definition, reverse causation and confounding by indication affect the association between antibiotic use in early life and development of wheeze or asthma		Overall OR 1.27 [95% CI 1.12, 1.43] and reduced to 1.12 [0.98, 1.26] when reverse causation and confounding by indication considered.
Heintze et al. [128] (2013) Germany	Systematic review	64 studies	To review the evidence suggesting an association between early childhood use of antibiotics and paracetamol and development of asthma		Studies showing a link between early use of antibiotics and paracetamol and development of asthma are likely to reflect bias.

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
Paracetamol					
Heintze et al. [128] (2013) Germany	Systematic review	64 studies	To review the evidence suggesting an association between early childhood use of antibiotics and paracetamol and development of asthma		Studies showing a link between early use of antibiotics and paracetamol and development of asthma are likely to reflect bias.
Etminan et al. [129] (2009) Canada	Systematic review	19 studies	To quantify the association between acetaminophen use and the risk of asthma in children and adults.		Increased risk of asthma and wheezing was observed following prenatal acetaminophen use OR 1.28 [1.13, 1.39] and OR 1.50[1.10, 2.05].
Eyers et al. [130] (2011) New Zealand	Systematic review	6 studies	To review the evidence from studies investigating the association between paracetamol use in pregnancy and childhood asthma		Any antenatal use of paracetamol was associated with an increase in risk of childhood asthma (OR 1.21 [1.02-1.44]).
Other maternal medications during pregnancy					
Kallen, B et al[131]	Longitudinal Study	685,015	To investigate the maternal use of drugs during the 2nd and 3rd trimesters with risk for	Childhood asthma was identified from the Swedish National Prescription Register and maternal drug	There was a positive association between risk of childhood asthma and maternal use of drugs for gastroesophageal reflux (adjusted OR 1.32 [1.12,1.55])

Study	Study Design	Characteristics of study population	Study objectives	Details of study	Key outcome(s)
(2013) Sweden			childhood asthma.	use during the latter part of the pregnancy from antenatal records.	and with opiates (adjusted OR 1.56 [1.05, 2.34]).
In Utero Exposures					
Li et al [132] (2011) USA	Longitudinal	734 pregnant women (offspring followed up until age 13)	To determine a possible link between exposure to electromagnetic fields in utero and development of childhood asthma	Women wore a metre for a 24 hour period during the first or second trimester of pregnancy to measure exposure to electromagnetic fields. Children were followed up until they were diagnosed with asthma or turned 13	A 1 unit increase in in utero electromagnetic exposure was linked with increased in likelihood of developing asthma by age 13 (HR 1.15 [1.04, 1.27]). Children whose mothers had a medium magnetic field level had a 74% increased rate of developing asthma (HR 1.74 CI 0.93 - 3.25) compared with those whose mothers had a low level. Children whose mothers had a high magnetic field level during pregnancy had more than a 3.5-fold increased rate of developing asthma (HR 3.52 CI 1.68 - 7.35)
Stolevik, SB et al[133] (2013) Norway	Longitudinal Study	114 children followed for 3 years	To determine whether prenatal exposure to polychlorinated biphenyls and dioxins from the maternal diet are associated with the development of immune-related diseases in childhood	Data was collected using an annual questionnaire and maternal intake of the toxicants was calculated using a food frequency questionnaire	Maternal exposure to dioxin-like PCBs and dioxin was found to be associated with an increased risk of wheeze at (OR 2.71 CI 1.21–6.04) at age 0-3. Maternal exposure to non dioxin-like PCBs was associated with increased risk of and wheeze (OR 3.20 CI 1.42–7.22) at age 0-3.

Donohue, KM et al[26] (2011) USA	Longitudinal Study	568 pregnant women followed up until children were 12 years of age	To determine whether BPA exposure is associated with increased risk of physician diagnosed asthma	Maternal spot urine samples were collected during the third trimester of pregnancy and from children at ages 3, 5 and 7. BPA urinary concentrations were measured.	Urinary BPA concentrations at ages 3, 5 and 7 were associated with increased odds of asthma. (OR, 1.5 [95% CI, 1.1-2.0], P = .005; OR, 1.4 [95% CI, 1.0-1.9], P = .03; and OR, 1.5 [95% CI, 1.0-2.1], P = .04 respectively. Prenatal urinary BPA concentrations were inversely associated with wheeze at 5 years.
Gascon et al[134] (2012) Spain	Longitudinal	1455 mother-child pairs	To examine whether in utero exposure to dichlorodiphenyldichloro ethylene (DDE) increases infant wheeze	Maternal serum levels of DDE, organic compounds and PCBs were measured during pregnancy. Mothers completed a questionnaire on their child's health at 12-14 months of age.	Wheeze (defined as any reported wheeze over the past 6 months) increased with every 10% increase in DDE concentration (RR 1.11 [1.00, 1.22]).
Spanier, AJ et al [135] (2012) US	Longitudinal Study	396 mother-infant pairs	To examine the relationship between prenatal BPA exposure and wheeze in early childhood	BPA concentrations in serial maternal urine samples were measured and parent-reported child wheeze was assessed every 6 months for 3 years. Generalized estimating equations with a logit link were used to evaluate the association	Mean prenatal BPA above the median was positively associated with wheeze at 6 months ((AOR) = 2.3; 95% confidence interval (CI): 1.3, 4.1) but not at 3 years (AOR = 0.6; 95% CI: 0.3, 1.1)

Table 2. Quality assessment score. Global rating 1=Weak; 2=Moderate and 3=Good

Study Ref.	Selection Bias	Study Design	Confounders	Blinding	Data Collection Methods	Withdrawals and Drop-outs	Global Rating
Jedrychowski [3]	1	1	2	3	1	1	2
Haberg[7]	2	2	2	1	2	2	2
Stolevik [25]	3	2	1	3	3	1	3
Tischer[36]	1	1	1	2	1	1	1
Bolte[58]	3	2	2	1	1	2	2
Phipatanakul[59]	3	2	2	2	1	1	2
Harley[65]	3	2	2	2	3	1	3
Patel[75]	2	2	2	3	3	2	3
Camargo[87]	3	2	2	2	1	1	2
Silvers[94]	2	2	2	2	1	1	2
Virtanen[102]	2	2	2	2	3	2	2
Wiiga[118]	1	2	2	3	1	2	2
Caudri[122]	3	2	2	2	1	3	3
Heintz[129]	1	1	2	2	2	2	1

Search strategy

1. Asthma/
2. wheeze.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
3. atopy.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
4. hayfever.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
5. Allergens/
6. Bronchial Spasm/
7. reactive airway disease.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
8. Bronchial Hyperreactivity/
9. environmental factors.mp.
10. environmental influences.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
11. environmental exposure.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
13. 9 and 12
14. 10 and 12
15. 11 and 12
16. 13 or 14 or 15
17. environmental tobacco smoke.mp.
18. 1 or 2 or 3 or 4 or 6 or 7 or 8
19. 17 and 18
20. in utero exposure.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
21. 17 and 20

22. maternal smoking.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
23. 18 and 22
24. parental smoking.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
25. 18 and 24
26. Cotinine/
27. 18 and 26
28. 18 and 21
29. 19 or 23 or 25 or 27 or 28
30. limit 29 to (english language and humans and ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)") and english and humans)
31. from 30 keep 1-599
32. Nitrogen Dioxide/
33. gas fire*.mp.
34. cooker*.mp.
35. hob*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
36. 32 or 33 or 34 or 35
37. 18 and 36
38. Volatile Organic Compounds/
39. cleaning agents.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
40. chemicals.mp.
41. glue*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
42. floor covering*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
43. dry cleaning.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
44. Chlorine/
45. swimming pool*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

46. Solvents/
47. Benzene/
48. resin*.mp.
49. varnish.mp.
50. Paint/
51. ethyl benzene.mp.
52. air fresheners.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
53. toluene.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
54. caulk*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
55. Formaldehyde/
56. 18 and 38
57. 18 and 39
58. 18 and 40
59. 18 and 41
60. 18 and 42
61. 18 and 43
62. 18 and 44
63. 18 and 45
64. 18 and 46
65. 18 and 47
66. 18 and 48
67. 18 and 49
68. 18 and 50
69. 18 and 51
70. 18 and 52

71. 18 and 53
72. 18 and 54
73. 18 and 55
74. 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73
75. Vehicle Emissions/ae, pc, to [Adverse Effects, Prevention & Control, Toxicity]
76. plastic$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
77. phthalate$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
78. flame retardant$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
79. plasticizer$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
80. plasticiz$ polyvinyl chloride.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
81. floor covering$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
82. adhesive$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
83. synthetic leather.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
84. toy$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
85. cosmetic$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
86. indoor dust.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
87. di 2-ethylhexyl phthalate.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
88. 18 and 75
89. 18 and 76
90. 18 and 77
91. 18 and 78
92. 18 and 79
93. pvc.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
94. 18 and 93
95. 18 and 81

96. 18 and 82
97. 18 and 83
98. 18 and 84
99. 18 and 85
100. 18 and 86
101. 18 and 87
102. outdoor source$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
103. ozone.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
104. sulphur dioxide.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
105. traffic.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
106. exhaust.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
107. coal fire$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
108. diesel.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
109. weather.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
110. 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109
111. 18 and 110
112. particulate matter.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
113. UFP$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
114. transport.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
115. industrial incineration.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
116. firework$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
117. bonfire.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
118. solid fuel.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
119. heating$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
120. cooking.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

121. candle$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
122. vacuum$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
123. hoover$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
124. resuspension.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
125. ingression.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
126. incineration.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
127. 112 or 113 or 114 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126
128. 18 and 127
129. NOX.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
130. 32 or 33 or 34 or 35 or 129
131. 18 and 130
132. curtain*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
133. carpet*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
134. 18 and 132
135. 18 and 133
136. 88 or 89 or 90 or 91 or 92 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 134 or 135
137. tetraethyl lead.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
138. 18 and 137
139. cerium oxide*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
140. 18 and 139
141. cold air.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
142. 18 and 141
143. meteorolog*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
144. 18 and 143
145. temperature.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

146. 18 and 145
147. climate.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
148. 18 and 147
149. 111 or 142 or 144 or 146 or 148
150. air pollut*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
151. 18 and 150
152. total suspended particulate*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
153. 18 and 152
154. coal.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
155. 18 and 154
156. wood.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
157. 18 and 156
158. peat.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
159. 18 and 158
160. biomass.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
161. 18 and 160
162. oil.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
163. 18 and 162
164. diacetyl.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
165. 18 and 164
166. 128 or 151 or 153 or 155 or 157 or 159 or 161 or 163 or 165
167. allergens.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
168. aspergillus.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
169. cladosporium.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
170. dust mite*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

171. cat*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
172. dog*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
173. horse*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
174. animal*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
175. pet*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
176. mould.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
177. mold.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
178. alternaria.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
179. cockroach*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
180. mice.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
181. rats.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
182. pollen.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
183. grass.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
184. aeroallergen*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
185. IgE.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
186. fungal spore*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
187. food allerg*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
188. glucan*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
189. peanut*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
190. egg.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
191. milk.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
192. dairy.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
193. 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192
194. 18 and 193

195. exercise.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
196. 18 and 195
197. lipopolysaccharide.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
198. 18 and 197
199. endotoxin.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
200. 18 and 199
201. respiratory syncitial virus.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
202. 18 and 201
203. rhinovirus.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
204. 18 and 203
205. influenza virus.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
206. 18 and 205
207. corona virus.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
208. 18 and 207
209. 202 or 204 or 206
210. diet.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
211. 18 and 210
212. sulphite*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
213. sulfite*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
214. sodium metabisul*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
215. monosodium glutamate.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
216. MSG.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
217. sodium benzoate.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
218. vitamin D.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
219. vitamin E.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

220. antioxidant*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
221. lipid*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
222. 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221
223. 18 and 222
224. 211 or 223
225. breastfeeding.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
226. weaning.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
227. 225 or 226
228. 18 and 227
229. drug*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
230. 18 and 229
231. aspirin.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
232. paracetamol.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
233. antibiotic*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
234. NSAID*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
235. 231 or 232 or 233 or 234
236. 18 and 235
237. obesity.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
238. 18 and 237
239. 29 or 131 or 136 or 149 or 166 or 194 or 196 or 198 or 200 or 209 or 224 or 228 or 236 or 238
240. 9 or 10 or 11
241. 18 and 240
242. 239 or 241
243. 74 or 242

244. limit 243 to (("all infant (birth to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)") and english and humans and (case reports or classical article or comparative study or congresses or consensus development conference or consensus development conference, nih or controlled clinical trial or "corrected and republished article" or government publications or guideline or historical article or introductory journal article or journal article or meta analysis or multicenter study or patient education handout or periodical index or randomized controlled trial or research support, nih, extramural or research support, nih, intramural or research support, non us gov't or research support, us gov't, non phs or research support, us gov't, phs or "review" or "scientific integrity review" or twin study or validation studies))

245. from 244 keep 6033,6045,6055,6062,6065,6091,6122,6150,6166,6172,6179,6225,6229-6230,6245,6249,6304,6307-6309,6315,6317,6346,6413-6414,6428,6435,6441,6453,6516,6551-6552,6574,6581,6585,6588,6599,6622,6641,6660,6699

246. from 244 keep 6710,6783

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not present
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	On line supplement
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	On line supplement
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Multiple outcomes described

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not appropriate

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	On line supplement
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Throughout results
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Pages 6-7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	On line supplement
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	On line supplement
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Pages 6-19, no forest plot as meta analysis not possible
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	See above
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	On line supplement
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Throughout results
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 19

PRISMA 2009 Checklist

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Pages 19-21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Pages 19-21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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